

# Abstractbook



## European Society of Magnetic Resonance in Neuropediatrics ESMRN

10th International Congress

September 3 – 5, 2009

University Hospital Zurich, Switzerland

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## Special morning lecture

### Normal pre- and postnatal brain development

J. Barkovich, San Francisco, USA

The central nervous system derives from the dorsal epiblast of the vertebrate embryo, and is induced by a combination of signals originating in the region of Hensen's node in the posterior margin of the early embryo<sup>1</sup>. After many steps, a neural tube is formed that subsequently develops a series of vesicles at its anterior (rostral) end. These three vesicles are designated the prosencephalon or fore-brain (which soon divides into diencephalon and telencephalon), the mesencephalon (midbrain), and the rhombencephalon (hindbrain), which divides into the rostral metencephalon (pons and cerebellum) and caudal myelencephalon (medulla oblongata). This differentiation along the anteroposterior (AP) axis (also called the rostral-caudal axis) is called patterning, a name given to the early differentiation of the neural tube<sup>2</sup>. Patterning similarly occurs in the dorsal-ventral axis; these two orthogonal processes result in the development of the protomap of the developing brain<sup>3,4</sup>. From this point onward, the brain develops as a result of the establishment of germinal zones, where cells are generated, cell migration, development and navigation of neurites through the developing brain, establishment of synaptic connections among neurites, the development of sulci, and, finally, refinement of synaptic connections; this latter process continues throughout life.

From an MRI perspective, we are most interested in brain development beginning at the middle of the second trimester, the time at which fetal MRI becomes diagnostic. The processes that can be evaluated by magnetic resonance techniques are<sup>1</sup> sulcation and myelination, which can be evaluated by MRI<sup>5,2</sup> development of the cerebral microstructure (which loosely corresponds to development of white matter tracts, maturation of synapses, and organization of the cortex, best evaluated by diffusion tensor imaging<sup>6-12,3</sup> maturation of cerebral chemistry (which is grossly evaluated by magnetic resonance proton spectroscopy<sup>13-20,4</sup> maturation of cerebral blood flow (evaluated by perfusion CT and MR imaging, single photon emission computed tomography, and positron emission tomography<sup>21,22; and 5</sup> maturation of glucose metabolism (best evaluated by fluorodeoxyglucose positron emission tomography<sup>23,24</sup>). These processes, and their evaluation by various imaging techniques, will be discussed in this lecture, along with general concepts of brain maturation.

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9:00-9:45

### **Intrauterine brain injury**

D. Prayer, Vienna, Austria

Acquired brain injury is defined as damage of a previously normally formed structure. On fetal MRI, acute and chronic manifestations or a combination thereof may be identified. While acute changes, such as ischemic infarction, hemorrhage, thrombosis and global brain edema are unequivocal signs of acquired brain injury, while chronic changes, as, for instance, widening of the ventricles, substance loss, and calcifications may be unspecific. In general, alterations of the fetal brain may be assigned to one of the following entities: anomaly (structural change without pathological significance), malformation, and acquired lesion including disruption (subsequent maldevelopment resulting from an acquired lesion). Pathological conditions, possibly leading to structural damage of the fetal brain include maternal factors, coagulation disorders, intoxication, metabolic disorders, mechanical and placenta-related injuries. In addition, intracranial malformations (as, for instance those of vascular origin) and extracerebral malformations (especially of the heart) may lead to subsequent ischemic/hemorrhagic impairment of the fetal brain. One of the main underlying reasons for acquired fetal brain pathology is infection. Signs of a so-called fetal inflammatory response syndrome, where extracerebral organs and the placenta may be involved, have to be recognized. Infective agents with affinity to the central nervous system may lead to characteristic lesion patterns that allow to draw conclusions on the respective agent. Even if T2-contrast is the mainstay of fetal MRI, other sequences, such as T1-weighted, echoplanar, diffusion-weighted, including tensor, and spectroscopy might be helpful in evaluating acquired fetal brain injury.

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9:45-10:30

### **Peri- and postnatal brain injury**

M. Rutherford, London, United Kingdom

The main aims of imaging the neonatal brain are to identify and characterise congenital or acquired abnormalities with the view to securing a diagnosis and a potential prognosis for the child. It is becoming increasingly important however to attempt to time an injurious process, to ascertain an aetiology and to understand the individual variation in lesion pattern and outcome with apparently similar clinical events and signs.

Imaging at 3 Tesla provides excellent detail of the brain allowing better definition of lesions and the ability to support advanced techniques such as DTI and angiography.

Current guidelines for neonatal brain imaging would recommend that for maximum lesion detection imaging is performed approximately one week from delivery or the perceived injurious event. Imaging at earlier time points necessitates the use of diffusion imaging, although this may still underestimate the size of a lesion particularly in the basal ganglia and thalami. There is a strong association between the clinical presentation and the pattern of injury. Neonates who develop an encephalopathy following a documented acute event such as uterine rupture or cord prolapse sustain lesions in the basal ganglia and thalami with the appearance of the intervening posterior limb being a good additional guide to later motor outcome. In infants with no such acute event white matter and cortical injury is more common usually in combination with the BGT lesions but sometimes in isolation.

Correlations with neurodevelopmental outcome are reliable provided good quality imaging is performed at the correct time. When the clinical presentation is not typical for the pattern of injury detected then caution must be exercised when attempting to predict outcome. For instance, in the term infant the presence of haemorrhage is unusual and the outcome may be poorer than predicted from the tissue injury alone. With atypical patterns of injury further investigations into the thrombophilic and the metabolic status of the infant should be made. In an encephalopathic infant it is easy to overlook dysmorphic features or unusual neurological signs that may suggest an alternative or additional diagnosis. There have now been several trials on the effect of hypothermia on modifying brain injury in term born neonates with hypoxic ischaemic encephalopathy. Whilst these have shown some improvement in short term outcome this has perhaps been less impressive than animal studies have suggested. Neonatal MR imaging may be a useful surrogate marker for outcome in interventional trials such as these and it is therefore important to ensure that the ability to predict outcome using neonatal imaging is not altered in the presence of the treatment.

Information about the timing of an injury can be obtained by serial imaging particularly combining diffusion and conventional imaging however the exact timing remains an approximation of what is most likely and still lacks the precision demanded of us by our medicolegal colleagues. Serial imaging can also provide us with novel insights into the brain's response following an acquired injury with diffusion tensor imaging providing ideal data to exploit with quantification methods such as probabilistic tractography and tract based spatial statistics (TBSS).

Lastly it is a sad reality that many of our neonates who sustain perinatal brain injury die. Postmortem examination should always be sought if only to confirm the diagnosis. A comparison of post-mortem imaging and histology may be extremely useful in aiding our image interpretation in addition to identifying the histological responses to the documented injury information that may improve future treatment strategies and the ability of MRI to provide monitor their effect.

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11:00–11:45

**Motor brain dysfunction: morphology – function relationship**

I. Krägeloh–Mann, Tübingen, Germany

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Cerebral Palsy can be regarded as a model to study morphology – function relationship and neuroplasticity with regard to motor function.

Typical pathogenetic patterns in early brain development characterize CP in more than 75%: in 9% malformations, in 56% periventricular lesions and in 18% cortico-subcortical lesions (basalganglia/thalamus lesions, parasagittal lesions and infarcts).

When looking at the subtypes of CP, malformations are seen in unilateral spastic CP (US-CP) in 10%, in bilateral spastic CP (BS-CP) in 16%, not in dyskinetic CP, in ataxic CP in 17%; periventricular lesions in US-CP in 60%, in BS-CP in 36%, in dyskinetic CP in 14%, cortical and deep grey matter lesions are seen in 15% in US-CP, in 34% in BS-CP and in 54% in dyskinetic CP; in ataxic CP in 17% are lesions reported – but not specified.

In the motor system functional deficit, illustrated on the example of periventricular lesions, seems tightly related to the extent of the lesions within the motor tracts. In contrast to the adult brain, abnormal fast conducting cortico-spinal projections from the healthy hemisphere exerting the primary motor control can be seen following large unilateral lesions disrupting motor tracts. Such ipsilateral projections constitute a specific compensatory mechanism of the young brain although their functional role seems to decrease already during late gestation. We could not find any evidence for inter hemispheric reorganisation within the sensory system.

The reorganisation processes, we could observe, always involved homotopic areas of the other hemisphere, we could not yet find clear evidence for heterotopic reorganisation neither intra- nor interhemispherically.

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11:45–12:30

**Encephalitis and related inflammatory brain disorders**

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**Pediatric brain infections**

**Introduction**

The central nervous system (CNS) and its covering membranes may be involved in a variety of infectious processes, either during intrauterine development or in the postnatal life<sup>1</sup>. Although the CNS is normally protected by the meninges and blood–brain barrier (BBB), it is more vulnerable to infectious agents than any other tissue, due to the lack of a true lymphatic system, the little resistance to infection offered by the subarachnoid space, and the fact that CSF facilitates infection spread over the brain and spinal cord and into the ventricles<sup>2</sup>. Furthermore, capillaries are absent in the subarachnoid space itself and there are tight junctions between intra- and extracranial venous system (i.e., without valves). Early recognition of CNS infection in the pediatric age group is extremely important due to the great potential for permanent damage in survivors. Magnetic resonance imaging (MRI) has greatly facilitated early diagnosis, and is today the gold standard in imaging of CNS infectious disorders.

### **Intracranial congenital infections**

#### **Cytomegalovirus infection**

Congenital CMV infection causes different neuroradiologic patterns, depending on the timing of infection during gestation<sup>5</sup>. However, it is not always easy to differentiate between early and mid-gestational infection, and some degree of overlapping may occur. Infections occurring earlier during pregnancy are characterized by lissencephaly, hypoplastic cerebellum, abnormal myelination, marked ventriculomegaly, and diffuse periventricular calcifications. Infections occurring in the middle of gestation cause polymicrogyria, impaired myelination, less evident ventricular enlargement, and less prominent cerebellar hypoplasia. Late congenital infections may determine symmetrical lobar white matter involvement, with or without calcifications. Because neuronal migration and cortical organization is already concluded, no significant cortical abnormalities are found<sup>6-8</sup>.

White matter involvement may appear either as reduction of its volume due to lack of formation, or as areas of T2 prolongation related to impaired myelination and/or destruction, or again as cystic formations. Intracranial calcifications appear as high density spots on CT, and may be seen as T1 bright, T2 dark foci on MRI in neonates and young infants<sup>4</sup>. They are typically located in the periventricular regions. Though usually widespread, even a single calcified spot may be sufficient to suggest the diagnosis.

On imaging, late CMV intrauterine infection, characterized by patchy to confluent abnormal myelination<sup>6,8</sup> may strongly resemble a metabolic disorder. Therefore, metabolic causes should be considered in the differential diagnosis. Among these, Aicardi-Goutières syndrome is characterized by the association of leukoencephalopathy and calcifications. CSF analysis, revealing the increased lymphocyte count typical of Aicardi-Goutières syndrome, will clear the view.

#### **Toxoplasmosis**

The spectrum of severity of the brain involvement in congenital toxoplasmosis ranges from mild cases, with only few periventricular calcifications and mild atrophy, to severe cases, showing marked, diffuse cerebral calcifications and destructive parenchymal lesions. Imaging findings show a gross correlation with the period of gestation at which maternal infection occurs. Calcifications are diffuse and involve the basal ganglia, thalami, periventricular parenchyma, and cerebral cortex<sup>3,4,11</sup>. Generally, albeit not invariably, calcifications tend to be more peripheral than in CMV infection. Ventricular dilatation of variable severity and areas of porencephaly may be seen<sup>4</sup>. There is typically a disproportionate dilatation of the posterior portions of the lateral ventricles with respect to the frontal horns, secondary to prevalent white matter destruction in these regions. Unlike with CMV, malformations of cortical development are not a typical feature of congenital toxoplasmosis.

#### **Neonatal herpes simplex virus infection**

Neonatal herpes simplex infection differs from other congenital TORCH group infections in that it is usually acquired during passage through an infected birth canal, while ascending and transplacental infection are much less common. Postnatal infections have been uncommonly reported<sup>12,13</sup>. The vast majority of congenital herpes virus infection (about 75-90%) are caused by the herpes simplex type 2 (HSV2) virus. This represents a notable difference from postnatal (i.e., childhood) herpetic meningoencephalitis, that are caused by the herpes simplex type 1 (HSV1) virus.

Neonatal HSV2 infection causes diffuse, nonspecific encephalitis characterized by edema and subtle, ill-defined patchy zone of enhancement<sup>35</sup>, eventually resulting in widespread brain destruction. There is rapid progression towards global brain involvement with brain destruction eventually leads to diffuse cerebral atrophy.

#### **Congenital human immunodeficiency virus (HIV) infection**

Transmission of HIV from infected pregnant women to their fetuses may occur either through transplacental passage of the virus (especially during the second or third trimester), during passage through an infected birth canal, or by ingestion of maternal blood. Fetal infection accounts for 25% of cases, and parturitional infection for the remaining 75%<sup>1</sup>. Postnatal infection due to transmission of HIV by breast feeding may also occur.

Routine neuroimaging studies in congenital HIV-infected patients may be initially normal<sup>15</sup>. However, progressive mineralizing vasculopathy, revealed by intracranial calcifications that primarily involve the basal ganglia, may be present at birth<sup>15</sup>. Subcortical calcifications are only found in patients

infected in utero and prevail in the frontal lobes. Cerebral atrophy is the most common finding in children with congenital HIV infection.

### **Bacterial meningitis**

#### **Neonatal bacterial leptomeningitis**

Although presentation is consistently by the first month of life<sup>1</sup>, two different clinical entities exist, differing in age of onset, clinical presentation, and prognosis. Early-onset sepsis/(meningitis) affects newborns in their first week (usually first 48 hours) of life, and late-onset (sepsis)/meningitis presents after the first 7 days of life.

#### **Acute bacterial meningitis in children**

Stages 1/2: Choroid plexitis/ventriculitis. Neuroimaging will show a characteristic triad, composed of (i) choroid plexus engorgement and adhesion to the ventricular walls, (ii) ependymal enhancement, and (iii) intraventricular debris layered in the dependent portion of the ventricles, usually the trigones or occipital horns of the lateral ventricle<sup>4</sup>. Hydrocephalus is commonly associated, usually due to obstruction of the cerebral aqueduct or fourth ventricular foramina.

Stage 3: Arachnoiditis. In the early stages of infection, arachnoiditis may be unrecognizable. One should be aware of the fact that the imaging hallmarks of arachnoiditis, i.e., enlargement of the subarachnoid space, and thickened, enhancing meninges may remain completely unseen during the natural history of bacterial meningitides in children, especially those cause by group B streptococci. When present, two distinct patterns of abnormal meningeal enhancement may be observed, i.e. dural enhancement following the inner contour of the calvaria and leptomeningeal enhancement extending into the depths of the cerebral and cerebellar sulci and fissures<sup>20</sup>.

Stage 4: Vasculitis. Despite vasculitic changes are particularly prominent by the second and third weeks, cerebral infarction may often be an early event. Lesions are most frequently due to venous occlusion by fibrinoid thrombosis, and are usually multiple and hemorrhagic. Preferential locations are the cerebral cortex and underlying white matter; however, the periventricular white matter and basal ganglia may be also involved. Arterial thrombosis is less common than venous thrombosis, although endoarteritis with intimal thickening and leukocyte infiltration does occurs<sup>4,18</sup>. Arteritis may result into both arterial infarcts, involving either large or small vessels<sup>4</sup>, and pseudo-laminar cortical necrosis. On imaging, either large cortical infarction, due to major vessels involvement, or multiple lacunar-type infarcts in the distribution of perforating vessels in the brainstem, basal ganglia, and white matter may be seen<sup>4</sup>. Cortical laminar necrosis appears as pseudo-gyral T1 and T2 hyperintensity showing gadolinium enhancement. MRA can show irregularity and narrowing of the arterial lumen when large- to medium caliber vessels are involved. When the process involves small arteries, diffuse paucity of peripheral vessels is detected.

Although venous thrombosis is an uncommon complication of meningitis, it does occur especially in case of superimposed dehydration<sup>4</sup>. MRA is the gold standard in the diagnosis of venous thrombosis. Venous thrombosis may be complicated by venous infarctions, that tend to involve the cerebral cortex and subjacent white matter, but also the central white matter and basal ganglia. Around 25% of venous infarcts are hemorrhagic.

Stage 5: Cerebral edema. Cerebral edema is primarily related to vasculitis, increased permeability of blood vessels, and BBB changes (vasogenic edema), but may be complicated by cytotoxic and interstitial edema<sup>1</sup>. In neonates, edema may be the initial manifestation of disease because of rapid evolution and greater vulnerability of the immature brain to the infectious agent. Cerebral edema is initially vasogenic due to vasculitis and increased permeability of blood vessels, but may become cytotoxic when parenchymal injury ensues. In most instances, CT scan will show obliteration of the basal cisterns, fissures, and cerebral and cerebellar sulci due to the presence of inflammatory exudate and brain swelling. The latter is characterized by poorly defined or slit-like ventricles, absence of subarachnoid spaces, and blurred gray-white matter junction.

#### **Cerebritis and brain abscess**

Abscess occurring in neonates and small infants have a number of peculiarities that distinguish them from those occurring in older children and adults. First, they are usually caused by gram-negative germs. Second, they are relatively large, often multiple, and typically incomplete, i.e., without a well-defined capsule, which favors their rapid enlargement<sup>21</sup>. Neonatal abscesses are located in the cerebral hemispheres, especially in the frontal and parietal lobes, and usually originate in the periventricular white matter, whereas the subcortical white matter and basal ganglia are more common locations in

older children<sup>18,22</sup>. Deeply located abscesses may rupture into the adjacent lateral ventricle<sup>4</sup>. Evolution from focal cerebritis to mature abscess with fibrous capsule usually occurs over a 2-3 week period, although such period may vary from a few days in neonates<sup>4</sup> to several months<sup>23</sup>. Four consecutive stages may be identified<sup>23-27</sup>.

### **Intracranial viral infections**

#### **Herpes simplex virus encephalitis**

MRI is the gold standard in diagnostic imaging of HSV encephalitis, being more sensitive than CT in detecting early changes and allowing better evaluation of the degree of CNS involvement. MRI shows prolongation of T1 and T2 relaxation times in the temporal lobe, insular cortex, orbital surface of the frontal lobe, and cingulate gyrus. Occasionally, the parietal lobes may also be involved<sup>34</sup>. T2-weighted and FLAIR images are most sensitive to areas of inflammatory swelling, appearing as high signal intensity lesions involving both the gray and white matter<sup>4,34</sup>. On T1-weighted images, multiple hyperintense areas representing petechial hemorrhage are commonly seen. After gadolinium administration there is a variable degree of enhancement, predominately involving the pial and cortical surfaces with a typical gyriform pattern. Usually, enhancement is not detected earlier than three days after clinical presentation<sup>34</sup>.

#### **Chickenpox**

The most common complication of varicella is acute cerebellitis occurring days to 2 weeks after the exanthema, usually resolving after weeks to months. Delayed onset of neurological deficits, usually characterized by acute contralateral hemiplegia sometimes associated with extrapyramidal symptoms, has been described 1-4 months after primary varicella or herpes zoster infection<sup>35-37</sup>. The postulated pathophysiological mechanism is a focal vasculitis. MR imaging shows basal ganglia infarcts, commonly unilateral. MR angiography may either be normal or show unilateral narrowing of the common carotid artery and of proximal branches of the anterior or middle cerebral artery<sup>36</sup>.

### **Imaging of acute disseminated encephalomyelitis**

#### **Background**

Acute disseminated encephalomyelitis (ADEM) is a monophasic demyelinating disease of the central nervous system typically affecting both the gray and the white matter of the brain and spinal cord in multiple locations. In the acute stages, ADEM is characterized histologically by perivenous edema, demyelination, and infiltration with macrophages and lymphocytes, with relative axonal sparing, whereas the latter course of the disease is characterized by perivascular gliosis<sup>1</sup>.

#### **Neuroimaging**

The neuroradiological findings of ADEM are not specific and typically do not allow differentiation of ADEM from multiple sclerosis or encephalitis. It is noteworthy that computerized tomography (CT) is typically unrevealing unless large lesions are present, in which case a faint hypodensity may be detected. As a consequence, in presence of suggestive clinical findings magnetic resonance imaging (MRI) should be obtained.

Conventional MRI findings typically include multiple, asymmetrically distributed, poorly marginated, hyperintense areas on T2-weighted and FLAIR images, whereas unenhanced T1-weighted images are usually inconspicuous unless the lesions are very large, in which case faint hypointensity is seen. Contrast enhancement is variable. In my personal experience, lesions of ADEM have only uncommonly been enhancing. This is especially true with small lesions, whose blood-brain barrier integrity is usually rapidly restored already in the acute phase of the disease. When present, contrast enhancement typically involves the vast majority of lesions simultaneously. In typical cases, multiple lesions that involve both the white matter and the deep gray matter nuclei (i.e., thalamus and basal ganglia) are detected<sup>5,7,9</sup>; in about 30% of cases, the cerebral cortex is also involved<sup>5</sup>. Regarding white matter lesions, the subcortical and deep white matter regions are more frequently involved than the periventricular white matter. Remarkably, radially oriented corpus callosum lesions (i.e., Dawson's fingers) are typical of MS while they are not commonly seen in ADEM. The white matter lesions are typically distributed asymmetrically, resulting in a leopard skin regional distribution. Conversely, involvement of the basal ganglia and thalami often has a symmetric appearance that may mimic the findings of

Leigh disease; deep gray matter involvement may be distinctive of ADEM and is a useful differentiating sign from MS<sup>10</sup>. It is remarkable that selective involvement of the cerebral cortex may be the only manifestation of ADEM, in the absence of any abnormality of the white matter. Involvement of the infratentorial compartment is seen in greater than 50% of cases. The brainstem, middle cerebellar peduncles, and cerebellar white matter may be involved. Lesion size and morphology is widely variable, although one lesion measuring at least 1 cm in diameter is often present<sup>9</sup>. Mass effect is often negligible, with a notable exception regarding brainstem involvement which may produce significant swelling, to the extent that an erroneous diagnosis of tumor may sometimes be considered. In the vast majority of cases, lesions appear simultaneously with clinical presentation and disappear with clinical recovery. However, delayed appearance of MRI abnormalities up to one month after clinical presentation has been described, suggesting that a normal brain MR scan obtained within the first days after the onset of neurological symptoms suggestive of ADEM does not exclude this diagnosis and that follow-up is advisable in presence of a strongly suggestive clinical evidence<sup>11,12</sup>. In most cases, lesions will resolve completely, albeit gradually, with steroid therapy, although MRI abnormalities may sometimes persist for longer periods or even become permanent<sup>1</sup>. At 6 months follow-up, ADEM lesions should resolve or remain unchanged; however, appearance of new lesions strongly suggests MS<sup>8</sup>.

About 30% of patients with ADEM will also show lesions in their spinal cord<sup>13</sup>. T2-weighted images may show multiple, more or less well-defined areas of increased signal intensity within the cord<sup>14</sup>. Some of these lesions may be confined to the gray matter, others are located in the white matter, and some involve both. Holocord involvement is possible. Segmental disease generally involves 2-3 vertebral bodies in length, and may expand the cord slightly. Lesions usually do not enhance with gadolinium chelate administration.

Advanced MR imaging modalities such as magnetization transfer imaging (MTI), diffusion-weighted imaging (DWI), and MR spectroscopy have recently been introduced in the diagnostic workup of patients with suspected ADEM, principally aiming at identifying early abnormalities in order to institute early treatment that may ideally improve the outcome. Particularly, MTI was proposed to play a role in the early diagnosis of ADEM, when conventional MRI is unrevealing. However, it has now been established that MTI fails to reveal abnormalities in the normal-appearing brain tissue in patients with ADEM<sup>15</sup>. DWI shows variable findings depending on the stage of the disease, with restricted diffusion in the acute stage (i.e., within 7 days of clinical onset)<sup>16</sup> and increased diffusion in the subacute stage (i.e., after 7 days of the onset)<sup>16,17</sup>. A possible explanation of these findings is that in the acute stage, swelling of the myelin sheaths, reduced vascular supply, and dense inflammatory cell infiltration may account for the reduced diffusivity, whereas in the subacute stage axonal loss, demyelination, and edema cause an expansion of the extracellular space which results in increased diffusivity<sup>16</sup>. However, the value of DWI in the early diagnosis of ADEM and in the differentiation from other entities remains as yet undetermined, since similar phenomena have been showed to occur in multiple sclerosis plaques<sup>18</sup>. Moreover, restricted diffusion does not appear to imply irreversible damage in ADEM.

MRS studies have not shown detectable changes in metabolite ratios in the acute stages of the disease; conversely, studies conducted in the subacute phase have shown reduction of N-acetylaspartate (NAA) in regions corresponding to the areas of high T2 signal intensity<sup>16,19</sup>. NAA reduction is probably related to transient neuroaxonal dysfunction rather than to irreversible neuroaxonal loss, as shown by evidence of NAA increase in follow-up studies, paralleling the normalization of conventional MRI findings<sup>19</sup>. Remarkably, choline levels are normal in the acute stage<sup>17,19</sup>, whereas an increase in choline is detected in the subacute stage<sup>16</sup>; this probably reflects absence of myelin breakdown during the initial stage, marking an important difference from MS as well as various leukodystrophies, in which choline is promptly elevated because of increased levels of the myelin breakdown products glycerophosphocholine and phosphocholine<sup>18,19</sup>.

#### Differential diagnosis

When assessing a patient with suspected ADEM, the most obvious concern is the differentiation from an onset of MS. This is a major problem for which there seems to be no established solution based on current knowledge. Studies have shown that approximately one fourth of patients with ADEM will develop a classical relapsing form of MS in the subsequent 2 to 5 years (27), but these patients are difficult to identify on initial presentation. However, a number of clinical, biological, and radiological differences between ADEM and MS may prove useful to advance a reasonable diagnosis (Tab. 1).

Firstly, MS only uncommonly affects individuals younger than 10 years. Unlike MS, ADEM is typically correlated with a viral prodrome and has a florid, polysymptomatic onset with attacks that fluctuate over a period of about 3 months. In ADEM, MRI shows at least one, large lesion whereas MS plaques are often smaller, although tumefactive plaques may represent the first clinical and radiological manifestation of MS, especially in the pediatric age group. Follow-up imaging will typically show resolution of the picture in ADEM, whereas new lesions are often detected in MS. Finally, CSF studies show increased white blood cell count in ADEM with infrequent oligoclonal bands, whereas MS is typically characterized by a normal white blood cell count with presence of oligoclonal bands<sup>11</sup>.

Table 1 - Differential diagnosis between ADEM and multiple sclerosis

	ADEM	Multiple sclerosis
Clinical picture	Widespread CNS dysfunction Fever, headache, seizures Common consciousness impairment Bilateral optic neuritis	Predominant unilateral involvement Motor deficit, cranial nerve palsies Rare consciousness impairment Unilateral optic neuritis
Precedent viral infection	Common	Uncommon
Course	Acute (monophasic disorder)	Chronic (polyphasic disorder)
CSF	Mild pleocytosis Rare intrathecal IgG production and oligoclonal bands	High and persistent pleocytosis Intrathecal IgG production (70-90%) Oligoclonal bands (90-95%)
MRI	Diffuse lesions Poorly marginated (partly due to edema) Uniform appearance Predominant subcortical/deep white matter involvement Corpus callosum usually not involved	Predominantly unilateral lesions Well marginated Variable appearance Predominant periventricular white matter involvement Corpus callosum typically involved
Gray matter involvement	Common	Uncommon
Contrast enhancement	Homogeneous in all lesions	Heterogeneous (related to different stage of evolution of the lesions)
Spinal cord	Transverse myelitis	Partial myelopathy
Response to steroid treatment	Decrease in number and size of lesions	No modifications of lesions
Follow-up MRI	Complete/partial resolution of lesions (residual gliosis and demyelination may occur) No new lesions	New lesions
Sequelae	Uncommon	Common

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14:15–15:00

**Gray matter: imaging, embryology, genetics**

J. Barkovich, San Francisco, USA

The cerebral cortex and deep gray matter nuclei of the cerebrum and cerebellum form as the result of three major processes: cell proliferation, cell migration, and cortical organization (a process that includes cell specification, the growth of neurites (axons and dendrites) that eventually form synapses, and the organization of the cortex into layers) [Guerrini, 2008 #2752; Barkovich, 2005 #2155; Kriegstein, 2004 #2052]. Disruption of these processes, either due to genetic mutations or prenatal injury/infection, results in a group of malformations known as malformations of cortical development (MCDs). A classification of these disorders is shown below.

- I. Malformations due to abnormal neuronal and glial proliferation or apoptosis
  - A. Decreased Proliferation/Increased Apoptosis or Increased Proliferation/Decreased Apoptosis – abnormalities of brain size
    1. Microcephaly with normal to thin cortex
    2. Microlissencephaly (Extreme microcephaly with thick cortex)
    3. Microcephaly with extensive polymicrogyria
    4. Macrocephalies
  - B. Abnormal Proliferation (abnormal cell types)
    1. Non-Neoplastic
      - a. Cortical hamartomas of tuberous sclerosis
      - b. Focal cortical dysplasia Type 2 (with dysmorphic neurons)
      - c. Hemimegalencephaly (HMEG)
    2. Neoplastic (associated with disordered cortex)
      - a. DNET (dysembryoplastic neuroepithelial tumor)
      - b. Ganglioglioma
      - c. Gangliocytoma
- II. Malformations due to abnormal neuronal migration
  - A. Classic Lissencephaly/Subcortical Band Heterotopia Spectrum
  - B. Variant Lissencephaly
  - C. Cobblestone complex/Congenital muscular dystrophy syndromes
  - D. Heterotopia
    1. Subependymal (periventricular)
    2. Subcortical (other than Band Heterotopia)
    3. Marginal glioneuronal
- III. Malformations due to abnormal cortical organization (including late neuronal migration)
  - A. Polymicrogyria and schizencephaly
    1. Bilateral polymicrogyria syndromes
    2. Schizencephaly (polymicrogyria with clefts)
    3. Polymicrogyria or schizencephaly as part of Multiple Congenital Anomaly/Mental Retardation syndromes
  - B. Focal cortical dysplasia Type 1 (without dysmorphic neurons)
  - C. Microdysgenesis
- IV. Malformations of cortical development, not otherwise classified
  - A. Malformations secondary to inborn errors of metabolism
    1. Mitochondrial and pyruvate metabolic disorders
    2. Peroxisomal disorders
  - B. Other unclassified malformations
    1. Sublobar dysplasia
    2. Others

Patients with MCDs can present with many clinical manifestations; most have developmental delay or epilepsy, while some have focal neurologic deficits. The diagnosis is usually made by neuroimaging, in particular by MRI. Sulcation is typically abnormal, with shallow sulci, abnormally thick cortex, ectopic

location of neurons, or irregularity of the surface of the cortex or the cortical-white matter junction. In certain disorders, such as lissencephaly due to ARX mutations, the basal ganglia are small and dysmorphic [Marsh, 2009 #2709]. In other disorders, such as variant lissencephalies [Jissendi-Tchofo, 2009 #2770] or the cobblestone complex of malformations (perhaps better called malformations secondary to gaps in the pial limiting membrane), the cerebellum is typically abnormal [Clement, 2008 #2561; Haltia, 1997 #1223]. The additional disorders can often help with specification of the malformation. This lecture will discuss the normal development of the cerebral cortex, the neuroimaging findings of the malformations, and the current knowledge of the genetic bases for them.

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15:00-15:45

### **White matter: imaging, embryology, genetics**

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The interhemispheric commissures are organized around the septum pellucidum. Their agenesis/dysgenesis is rarely isolated and typically reflects a more global white matter, or grey and white matter derangements. With modern imaging more attention is paid to the white matter, and malformations seem to be fairly common.

### **Anatomy**

The telencephalic commissural system

- The anterior commissure (paleocortical "olfactory" commissure) primarily connects the olfactory bulbs and amygdalae, but also covers significant parts of the limbic and neo-cortical temporal lobes. It is located in the superior part of the lamina terminalis.
- The hippocampal commissure (archicortical commissure) connects the entorhinal/parahippocampal cortices. It is stretched between the fornix crura and on the midline is fused to the inferior aspect of the corpus callosum, behind the septum pellucidum.
- The corpus callosum (neocortical commissure), comprises from front to back, a genu, body, isthmus and splenium; below the genu, the rostrum and lamina rostralis attach it to the anterior commissure; it is fused posteriorly with the hippocampal commissure. Grossly stated, the rostrum and lamina rostralis connect the associative orbitofrontal cortex; the genu, the associative prefrontal cortex (including anterior cingulate); the body, the precentral cortex; the isthmus, the sensory-motor strips; the splenium, the parietal, occipital and temporal neocortex (with the PTO associative area). Most callosal fibers are reciprocal homotopic; heterotopic fibers may connect cortical as well as subcortical gray matter.
- The septum pellucidum is a bilateral sheath of white matter (posterior to the septal cortex and nuclei). Its fibers form the perforate septo-cingulate tract that connects the septal and cingulate cortices through the corpus callosum, as an anterior fan-like extension of the longitudinal fornix.
- Other main white matter tracts
- The projection tracts, from the cortex to the brainstem or spinal cord, between the cortex and striatum and between the thalamus and cortex (corona radiata) are not readily identifiable on standard MR images but can be singled out by DTI
- This is true for the association tracts as well, either deep (inferior occipito-frontal, superior occipito-frontal) or long superficial (cingulum, arcuate/superior longitudinal, inferior longitudinal, uncinate) and short superficial.

### Embryology

In general, the development and progression of the axons forming the white matter depend on multiple factors: extracellular matrix environment, short and long range attractant and repellent substances, adhesion and fasciculation substances, guiding cells. Things become still more complex when the midline must be crossed, as the environment that was attracting the growth cone on one side must repel it on the other side so that it can continue its course.

Regarding the interhemispheric commissures, things happen differently for the anterior commissure and for the dorsal commissural plate (corpus callosum and hippocampal commissure). It all starts during weeks 9-11.

- The anterior commissure proceeds across the midline through the upper part of the lamina terminalis, where the two hemispheres are in continuity with each other; specialized cells there form cellular channels that guide the anterior commissural axons.
- The development of the commissural plate is more complex as the fibers must exit the hemisphere to cross the midline within the solid connective tissue of the meninx primitiva. The two hemispheres form a fusion line with a sling of specialized glia, along what is described as the cortico-septal boundary (junction line between the future cingulate cortex and the future septum pellucidum). There, pioneering callosal axons (from the cingulate gyrus) cross anteriorly, and, independently, the pioneering hippocampal axons cross posteriorly. There are therefore two initial commissural sites (three if the anterior commissure is included). On their way to the midline the pioneering fibers are hemmed-in by chemorepellents from two specialized structures, the indusium griseum and the glial wedge. Later callosal fibers progress by fasciculating along the pioneer fibers of both the anterior callosal and the posterior hippocampal commissures, the posterior callosum forming a single mass with the hippocampal commissure. Both the anterior and posterior segments finally join to form a single continuous commissural plate. Still later the anterior rostrum and lamina rostralis develop inferiorly toward the anterior commissure, closing anteriorly the space between the leaves of the septum pellucidum. This is essentially finished by mid-gestation

At the same time, the primordium of the septum pellucidum is involved in the process. The cortico-septal boundary is crossed transversely by callosal fibers. Between the anterior septal and the cingulate cortices, the fan-shaped septo-cingulate ipsilateral fibers course within the septum pellucidum and perforate the commissural plate. The inferior edge of each septal sheath contains the fibers of the ipsilateral longitudinal fornix. Posteriorly, the hippocampal commissural fibers of the fornix use the primordium of the septum pellucidum to reach the cortico-septal boundary where they cross toward the other side.

This development has two consequences: 1) the septum pellucidum is not a simple membrane: it contains the ipsilateral septo-cingulate fibers anteriorly, and the hippocampal commissural fibers posteriorly; 2) as already emphasized by Rakic and Yakovlev in 1968, the corpus callosum does not develop from the front to the back. Its anterior and posterior portions originate independently (the posterior in association with the hippocampal commissure) and fuse together secondarily. This explains that anterior only, or posterior only agenesis may exist. Or the presence of a posterior callosum in lobar HPE, where the hippocampal commissure has no reason not to develop. Or the anterior and posterior callosum separated by a dorsal cortical interhemispheric continuity ("fusion") in a syntelencephaly.

A last important point: in the last trimester of gestation and early post natal life, the commissural axons temporarily connect to the neurons of the transient (and selectively vulnerable) subplate which serves as a waiting zone until the cortex is ready to get connected.

### Malformations of the commissures

Pure classic commissural agenesis, complete ("complete agenesis of corpus callosum"). The commissural (callosal and hippocampal) plate is lacking altogether; in 50% the anterior commissure is lacking also. The commissural fibers are actually heterotopic rather than agenetic as they course dorso-ventrally in the septum pellucidum on each side and form the bilateral parasagittal Probst bundle. Instead of connecting symmetric points of both hemispheres, they connect different regions of the same hemisphere. Other essential bundles are agenetic or dysgenetic. The cingulum, that runs into the entorhinal/parahippocampal/cingulate gyrus is missing or hypoplastic, explaining the Y shape of the coronal section of the temporal horn, and the abnormal sulcation of the cingulate cortex.

The so-called colpocephaly (exceedingly large ventricular atria) may be explained by the lack of intrinsic occipital visual tracts (and not by the lack of commissural fibers as the Probst bundle is present).

Pure classic commissural agenesis, partial ("partial agenesis of corpus callosum").

The anterior corpus callosum is morphologically complete (often hypoplastic, though), the hippocampal commissure and associated posterior callosum are missing. Interestingly, Probst bundle, cingular abnormalities and colpocephaly are seen posteriorly, not anteriorly.

Complex classic commissural agenesis, complete or partial. The main features are the same, but associated with other CNS malformations: mostly periventricular nodular heterotopia, other malformations of cortical development, malformations of cerebellum, dysplastic brainstem, colobomas, hypothalamo-pituitary defects etc.

Commissural agenesis/dysgenesis with interhemispheric cysts. A major dysplasia of the interhemispheric meninges is observed with single or multiple meningeal cysts. Complex cortical malformation is common with subcortical nodular heterotopia and pseudo-PMG cortex. The Probst bundle may be missing on the side of the dysplasia. This group can be further divided in subtypes, including the Aicardi syndrome.

Commissural agenesis with interhemispheric lipomas. The lipomas also reflect a meningeal dysplasia, which is itself the likely cause of the commissural defect rather than the lipomatous mass (linear, nodular, tela choroidea type).

Isolated agenesis of individual commissures are uncommon: anterior commissure; corpus callosum, complete or partial; hippocampal commissure.

### **Other malformations of the white matter**

Septo-optic dysplasia (SOD) is characterized by an absent/partial septum pellucidum, a fusion of the fornices (common fasciculation?), an anterior optic pathway hypoplasia (rather than atrophy) and typically a significant ventriculomegaly. Corpus callosum and hippocampal commissures are usually (not always however) well developed. SOD may be pure, or complex associated with periventricular nodular heterotopia, hypothalamo-pituitary disorders, PMG and/or schizencephaly, rhombencephalosynapsis etc.

CRASH syndrome (for X-linked Callosal agenesis, mental Retardation, Adducted thumbs, Spasticity, Hydrocephalus) is characterized by a commissural agenesis, pyramidal tract agenesis, and a ventriculomegaly. It is a defect of a fasciculation gene, L1CAM on Xq28.

Syndromic craniosynostoses are commonly associated with white matter malformations: commissural agenesis (Apert), septal agenesis (Crouzon), hypoplastic mesiotemporal white matter. They are related to defects of FGFR genes which are co-agents of the fasciculation processes together with L1CAM.

Chiari II/MMC. In a significant number of cases, the white matter abnormalities in Chiari II malformations are not explained by hydrocephalus alone. The commissural dysgenesis is particular: sometimes severe it is never complete and never associated with a Probst bundle. The septum pellucidum may be hypoplastic, which is not expected in conjunction with hydrocephalus. An aberrant supracallosal cingular bundle is often found, and a ventriculomegaly may be present even before the development of hydrocephalus.

Idiopathic mental delays often demonstrate white matter abnormalities: thin or dysgenetic, or ill shaped corpus callosum, ventriculomegaly, prominent occipital horns (not expected in children), squaring of the lateral angle of the frontal horns.

### **Conclusion.**

The best recognized malformation of white matter is the so-called agenesis of corpus callosum. But this disorder, rather than a malformation, should be understood as a particular feature possibly associated with different disorders (not unlike the seizures, or a fever that may reveal many different diseases). OMIM quotes 130 syndromes of which "callosal agenesis" is a part. The clinical impact and the fine features of the malformation obviously depend on the cause of the syndrome. Modern imaging methods and better genetic understanding may lead to the recognition of more examples of specific white matter defects.

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16:15-17:00

**Pathology and pathogenesis of epilepsy**

R. Spreafico, Milan, Italy

Spreafico Roberto and Tassi Laura

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Cortical malformations, otherwise termed as Malformations of Cortical Development (MCD), are defined in their broadest sense as malformative lesions of the cortex resulting from developmental derangements of normal processes that take place during the first two trimesters of human pregnancy and involving cells that under normal circumstances participate in the formation of the cortical mantle. The pathological features of MCD, recognized by neuropathologists since the end of the 19th century and now attributed to different defects of building cortex, largely depend on the timing of the defect in the developmental processes as well as on its cause.

The aetiology of malformative disorders is often uncertain and the mechanisms by which they generate epilepsy are not completely understood, however over the past decade, molecular biologic and genetic studies of cortical development have greatly expanded our knowledge of the normal mammalian brain's development and derangements. Several disorders of cortical development have been recognized, and for some of them specific causative genetic defects have been identified.

The advent and development of imaging techniques has had a great diagnostic impact in this area, it has allowed the investigators to recognize MCD in vivo and have been helpful in providing correlations between imaging features, neuropathological picture and electroclinical findings related to epilepsy

In most of the patients with MCD epilepsy represent a prominent clinical aspect that frequently challenges the neurologist. Although seizures might occur at any age, they generally start in childhood and in many cases may contribute to worsening the developmental delay.

Although the statistical incidence of MCD in surgically treated patients varies among different centres, biased by different factors such as methodological approaches, patient's selections, MRI and neuropathological diagnosis, it is estimated that 25%-40% of drug resistant childhood epilepsies are due to MCD and that 75% of patients with MCD will have epilepsy sometime in their life

Since epileptic seizures are the consequence of abnormal electrical discharges arising predominantly from the cortical areas, it is evident why MCD are often associated with recurrent seizures frequently resistant to pharmacological treatment. Epileptic fits in patients with MCD are presumably a consequence of an imbalance between excitatory (glutamergic) and inhibitory (GABAergic) systems derived from the presence of a disorganized neuronal network. This abnormal circuitry may be restricted within the malformed cortical area or involving adjacent areas anatomically and functionally related to the disorganized cortex.

A dysfunction of synaptic circuits seems to be responsible for the abnormal synchronization of neuronal populations underlying the genesis of epileptiform activity in FCD and abnormalities in the morphology and distribution of local-circuit GABAergic neurons have been reported particularly in type II FCD that is the most investigated type of dysplasia.

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17:00-17:45

### **Advanced diagnostic imaging of epilepsy**

E. Widjaja, Toronto, Canada

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Intractable seizures can have a devastating effect on the development of a child. In children with intractable epilepsy that is refractory to medication, surgical treatment may be necessary. MRI is an essential imaging tool to assist in the identification of an epileptogenic substrate. High resolution, multi-planar and multiple sequences should be done so as to improve detection of subtle lesions such as focal cortical dysplasia. The interpretation of MR should be done in the context of clinical knowledge of the seizure semiology and EEG findings. Quantitative processing of 3D T1 weighted imaging allows assessment of cortical thickness, gray white matter blurring and gray matter density, which could potentially be used to identify subtle focal cortical dysplasia.

Additional MR imaging techniques such as diffusion tensor imaging (DTI) and MR spectroscopy have the potential to identify subtle lesions that are considered as MRI-negative. We have previously found DTI identified abnormal white matter beyond the MRI-visible focal cortical dysplasia, which can potentially assist in detecting the MRI-occult abnormalities within the epileptogenic zone. These additional imaging modalities can provide insight into the pathophysiology of malformations of cortical development.

In addition to lesion localization, identification of eloquent cortex and white matter tracts are an essential component of epilepsy surgery work-up so as to minimize functional deficit. The location of eloquent cortex can be mapped using functional MRI or magnetoencephalography (MEG). Functional MRI maps the sensori-motor cortex and also lateralizes language. Diffusion tensor imaging tractography can be used to map the eloquent white matter tracts including the corticospinal tracts and optic radiations. The eloquent cortex may be reorganized due to the presence of long-standing epileptogenic substrates such as malformations of cortical development or perinatal insult. In such cases, a functional approach tractography, that is, using the functional location of the eloquent cortex as defined using functional MRI or MEG, should be used as seed point of fiber tracking. Identification of the optic radiations is particularly relevant to temporal lobe resection as the Meyer's loop can be variable in different individuals.

In addition to MRI, MEG and nuclear medicine studies such as positron emission tomography (PET) and single photon emission computed tomography (SPECT) may be used to lateralize seizure focus and to guide placement of invasive intracranial electrodes. MEG dipole cluster has previously been shown to correspond to the epileptogenic zone as assessed using invasive intracranial monitoring. PET may demonstrate a larger area of hypometabolism compared to invasive intracranial monitoring identified epileptogenic zone, as PET demonstrates the epileptogenic network, which covers a larger area compared to the epileptogenic zone.

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8:15-9:00

### Special morning lecture

#### Significance of spontaneous brain activity – structure, development and function

A. Kleinschmidt, Gif/Yvette, France

Functional magnetic resonance imaging has had a major impact on the cognitive neurosciences. In the dominant mainstream, these data are analysed by estimating in a mass univariate framework parameters of a general linear model for condition-related activity changes. However, this approach neglects or discards two important sources of information. One is the information coded in the pattern of small voxel-by-voxel variations of signal, the other the trial-by-trial variability of ongoing activity levels prior to evoked responses. Arguably, the two most exciting developments in the past couple of years exploit these two sources of information. This talk will provide an overview with respect to the latter aspect. The demonstration of spatiotemporal structure in ongoing brain activity by so-called resting-state studies has triggered several new avenues of research. Some studies have dealt with the relationship between structural and functional connectivity. Others have explored developmental aspects and probed the relation between spontaneous activity and conditions of experimentally or clinically altered brain activity. Finally, a series of experiments have addressed the functional significance of spontaneous brain activity. In particular, the latter have yielded findings that need to make us change the way in which we build our concepts of brain function and accordingly the way in which we analyze brain function by neuroimaging means.

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9:00-9:45

#### Principles of developmental and adaptive changes of neuronal networks in neurocognition

L. Jäncke, Zurich, Switzerland

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9:45-10:30

#### Development of language functions – normal reading and dyslexia

D. Brandeis, Zurich, Switzerland

Departments of Child and Adolescent Psychiatry, University of Zurich, Switzerland and Central Institute for Mental Health, Mannheim, Germany

How language functions develop can serve as a prototype for higher brain functions and for uniquely human skills. The spatial distribution of the basic networks supporting speech perception including some hemispheric asymmetries evolves early in infancy, with the spatial extent of activation best seen by fMRI. However, subsequently the network's speed and specialization changes, paralleling massive developmental changes regarding metabolism and performance. These changes continue well into adolescence and are best seen through EEG-based measures. It is particularly intriguing that similar developmental stages characterize the subsequent development of the reading network, an evolutionary late achievement. The rapid initial tuning of a fast, print sensitive network during reading acquisition is prominent in EEG based measures. This initial tuning is delayed in Dyslexia, a specific developmental reading disorder. Developmental work illustrates the many facets of brain plasticity, and that a disorder like dyslexia may partly reflect reduced plasticity.

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11:00–11:45

### Development of number processing – normal calculation and dyscalculia

K. Kucian, Zurich, Switzerland

For many of us, numbers consume our daily lives: phone numbers, dates, access codes, prices. How does our brain process all these numbers?

A wealth of evidence indicates that humans and other animals have an innate sense of approximate numerical magnitudes – a “number sense”. Recent research showed that already 4 month olds are able to detect changes in the number of objects and that recruited brain regions map onto the same areas activated by adults suggesting early functional biases in brain organization that may channel subsequent learning to restricted brain areas (Izard, Dehaene-Lambertz, & Dehaene, 2008). Brain imaging studies in school-aged children strengthen the high overlap of the activated fronto-parietal network for number processing between children and adults, but show concurrent developmental changes according to increased expertise and performance of math skills (Ansari & Dhital, 2006; Kucian, von Aster, Loenneker, Dietrich, & Martin, 2008; Rivera, Reiss, Eckert, & Menon, 2005). Results provide evidence for a developmental process of increased functional specialization of the parietal cortex in numerical cognition, accompanied by decreased dependence on memory and attentional resources attributed to frontal areas.

Developmental impairments of number processing may be associated with atypical specialization of cortical regions underlying the most basic aspects of numerical cognition. In fact, morphometric and functional imaging studies in children with developmental dyscalculia, a specific impairment of number processing in otherwise typically developing children, point to a deficient development of neural representations of numbers. They show aberrant activation of brain regions specific for number processing, like the intraparietal sulcus, as well as, reduced gray matter density in the same parietal region and frontal areas (Kaufmann et al., 2009; Kucian et al., 2006; Mussolin et al., 2009; Price, Holloway, Rasanen, Vesterinen, & Ansari, 2007; Rotzer et al., 2008).

On the grounds of the high prevalence of developmental dyscalculia around 3–6% and the psychological strain of affected children, interventions based on scientific results are vital (Shalev & von Aster, 2007). We have developed a computer-based training to improve spatial numerical representation. Preliminary results of the evaluation of training effects by means of functional magnetic resonance imaging and neuropsychological testing indicate significant improvement of spatial representation of numbers in children with and without developmental dyscalculia, as well as, neuroplastic changes reflecting automation processes.

In recent years, we started to get a vague idea about developmental differences of the neural scaffolding for numerical cognition between children with and without developmental dyscalculia and future studies are needed to clarify and define developmental trajectories of this learning disability on which diagnostics and therapy can be supported.

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11:45-12:30

**Development of higher visual function – normal visual perception and visuo-motor deficits**  
P. Klaver, Zurich, Switzerland

Very low birth weight (VLBW) born children have a high prevalence to develop cognitive and motor disorders as well as visuo-perceptual deficits. Structural abnormalities have been reported for this group in wide spread cortical networks and white matter structures, particularly around the periventricular regions, in which posterior ascending tracks to the parietal lobule prevail. The mechanisms of functional neural development in VLBW adolescents are largely unknown. Here, results will be presented on a VLBW cohort (<1250 grams) that was born between 1992 and 1994 at the Children's University Hospital Zurich and who participated in a prospective longitudinal study. At the time of investigation they were between 13 and 15 years old. Controls participants (best friends) were matched for IQ, age, and social background. All participants were assessed for general neuropsychological abilities, visual perceptual, visuomotor integration, and motor skills. In addition, functional brain imaging data were acquired to assess high order visual perceptual functions, such as perception of moving point-light dots that generated 3D structures ("structures-from-motion") or moving human beings ("biological motion"). Neural activity was also measured during perception of animal and tool pictures to assess visual semantic category specific neural networks. We will show evidence for largely typically developing visual neural networks in VLBW adolescents at almost normal cognitive achievement. Impaired performance was found only for visual perception, peg board motor behaviour, and mental rotation skills. Reduced neural activation in VLBW adolescent parietal cortex was found during perception of structures-from-motion, biological motion and tool pictures, as well as of enhanced neural activation in frontal cortex during perception of structures-from-motion, biological motion and animal pictures. These results will be discussed in terms of the dorsal vulnerability hypothesis."

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14:15-15:00

**DTI, tractography and connectivity**  
J. Hennig, Freiburg i. Br., Germany

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15:00-15:45

**DTI and functional imaging in neonates, infants and small children**  
L. Hertz-Pannier, Paris, France

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16:15–17:00

### **Functional imaging of developmental and adaptive changes in neurocognition**

WD. Gaillard, Washington, D.C., USA

Imaging development of cognitive systems and their perturbation by disease and developmental disorders is challenging in paediatric populations. Using language systems as a model, the session will discuss the several experimental and analysis strategies that have been used to examine normal development of language networks. Review of current data on language system expression finds the networks that sustain language are fundamentally set by age four years; there are minor but important differences that suggest frontal systems are not firmly established until middle childhood and thus more malleable in response to brain insult. The session will then address the issue of heterogeneity, specifically the importance of identifying normal variant activation patterns and pathological variant activation patterns of atypical language dominance and representation. The constraints and developmental limitations for compensation and adaptation will be discussed. The methods used to examine heterogeneity will be reviewed and include: region of interest, regression, difference maps, penetrance, and principal component analysis. Results from recent studies suggest that "reorganization" of language systems represents a persistence of developmentally immature language systems, and that recruitment of areas outside of homologues and margins of traditional language processing networks is rare.

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17:00–17:45

### **Reparative plasticity (injury and recovery): What do DTI and functional imaging of prematurely born children tell us?**

L. Ment, New Haven, CT, USA

L.R. Ment, W.C. Allan, B.R. Vohr, R.T. Constable, A. Reiss, B.S. Peterson, R.W. Makuch, Yale University School of Medicine, Brown University, Maine Medical Center, Columbia University and Stanford University

Preterm birth results in significant disability, yet recent data suggest some recovery from injury of language systems in the prematurely-born. The underlying alterations in brain development responsible for these changes and the early biomarkers predicting them remain poorly understood. The advent of magnetic resonance imaging (MRI) has demonstrated that cortical gray matter, cortical white matter and deep gray matter volumes are all lower in the prematurely-born in the newborn period, at school age and during adolescence, but recent advances in MR imaging, including functional MRI (fMRI) with functional connectivity analyses, diffusion tensor imaging (DTI) and image analysis tools such as automatic voxel based morphometric (VBM) analysis methods for whole brain comparisons provide microstructural evidence of the dynamic interaction of injury and recovery in the developing brain.

Fractional anisotropy (FA), a DTI measure of axonal coherence, is linearly related to gestational age at birth, and VBM analyses suggest that this relationship persists through adolescence and young adulthood. Regional FA is sensitive to white matter injury in the newborn period, but may increase in response to environmental stimulation. Finally, this important microstructural measure is significantly correlated with cognitive outcome in the newborn period and may be used to explore the influence of preterm birth on language systems at school age and beyond.

Similar to FA values of diffusion tensor imaging, preliminary data suggest plasticity of the blood oxygen dependent signal (BOLD) of functional imaging in response to focal injury in the newborn brain. Functional imaging studies of prematurely born subjects and matched term controls at school age and adolescence demonstrate that preterm subjects are more likely to activate right hemisphere networks for both language and memory than term control subjects. Functional connectivity studies confirm the engagement of alternative neural systems for language in the prematurely-born, and the relationship between alternative connectivity and cognitive measures is just beginning to be explored. Finally, preliminary data suggest that functional connectivity subserving language may be explained in part by white matter volumes and regional FA values in the developing preterm brain. Emerging magnetic resonance imaging strategies provide important information about connectivity in the premature brain. Both DTI and the BOLD signals of functional imaging are directly related to the gestational age for preterm subjects, and numerous studies describe the impact of preterm birth on microstructural connectivity in the developing brain. Significantly, these early indicators not only correlate with outcome in the newborn period and early childhood but are also found in children born preterm both at school age and adolescence. They may serve as biomarkers for injury and recovery in the prematurely-born.

This work was supported by NS 27116 from the National Institutes of Health.

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8:15-8:45

**Honorary lecture – 10th biennial congress of the ESMRN**

J. Valk, Amsterdam, Netherlands

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8:45-9:30

**Special topic – Network concepts in normal brain function and in functional brain disorders**

R. Llinás, New York, USA

Thalamic and cortical neurons are richly and reciprocally interconnected and support recurrent functional loops in the intact brain. While the functional role of this circuitry in global brain function is still poorly understood much has been gained in recent years. Indeed, evidence will be presented from cellular, functional neuroimaging and clinical domains -- that thalamocortical resonance is not only a prerequisite for normal cognition, but that its perturbation, in a dynamic sense ( e.g. a dysrhythmia) can underlie a variety of neurological and psychiatric disorders.

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9:30-10:15

**Neural networks in childhood epilepsy: evidence of and possible implications for treatment**

M. Siniatchkin, Kiel, Germany

Simultaneous recording of EEG and blood oxygenation level-dependent (BOLD) functional MRI (EEG-fMRI) is a new promising non-invasive imaging tool that may be applied in patients with epilepsy to investigate hemodynamic changes associated with interictal epileptiform discharges (IED) and ictal epileptic activity. EEG-fMRI was successfully used in paediatric patients suffering from epilepsies to characterize individual as well as syndrome-specific epileptogenic networks. Although different confounding factors such as sedation and sleep during the investigation, variability of hemodynamic responses, and head movements may influence sensitivity of EEG-fMRI recordings in children, results of first studies demonstrated a sufficient correspondence between regions of BOLD activation / deactivation and areas of focal epileptic activity. In most children with focal epilepsies, however, EEG-fMRI revealed extended haemodynamic responses which were difficult to interpret without an appropriate reference. The application of both EEG source reconstruction and EEG-fMRI may substantially improve our knowledge about areas of generation and propagation of epileptic activity in a particular patient. So far, EEG-fMRI may be used to generate hypotheses about the epileptogenic zone within the presurgical setting in some patients. Moreover, EEG-fMRI technique has a potential to disclose syndrome-specific neuronal networks. Slow activity in hypsarrhythmia was correlated with activation in brainstem and putamen, areas specifically related to West syndrome. Both primary and secondary generalized paroxysms (absences, polyspike and wave discharges) were associated with a specific pattern of thalamic activation and deactivation of "default mode"-areas and caudate nucleus. Polyspikes in Lennox-Gastaut syndrome were linked to a pronounced activity in the thalamus and brainstem. Continuous spikes and waves in slow sleep (CSWS) were associated with a bilateral activation of insula, cingulate gyrus and temporal cortex and deactivation in the "default-mode" network. It seems likely that different epileptic syndromes and encephalopathies are characterized by a specific fingerprint of haemodynamic changes which may be used in diagnosis and evaluation of treatment. Despite of progress, further studies are needed to increase sensitivity and prove validity of EEG-fMRI recordings, to explain physiological significance of deactivations, and to improve localization potential of the technique within the framework of the presurgical epilepsy diagnosis.

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10:45-11:30

**Functional networks underlying epileptic discharges using EEG, fMRI and DTI**

L. Michels, Zurich, Switzerland

In my talk I will give first an overview about recent findings in epilepsy research using functional brain imaging methods such as EEG, fMRI and EEG-fMRI. For the latter, I will focus on functional networks properties before, during and after epileptic discharges. This is followed by recent EEG and EEG-fMRI findings from our research group. The results will be discussed in the framework of thalamo-cortical interaction in brain state regulation during normal development and in epilepsy. Finally, I will describe findings on own data using simultaneously EEG-fMRI recordings during cognitive tasks in healthy subjects and give an outlook how these results might be integrated in the context of epilepsy research.

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11:30-12:15

**Pathophysiology of childhood absence epilepsy: from genes to neural networks**

V. Crunelli, Cardiff, United Kingdom

My lecture will summarize current views on the genetics and pathophysiology of typical absence seizures, as observed principally in Childhood Absence Epilepsy. Specifically, I will review the following points:

1. Although there is strong consensus in describing typical absence seizures as a familial disease with a complex genotype, their precise genetic abnormalities have not yet been fully uncovered. In particular, mutations in T-type calcium channel genes do not appear to be as widespread as originally suggested.
2. The notion that typical absence seizures are truly 'generalized' from their very start has been recently challenged by observations in humans and animals that seizure onset is associated with paroxysmal activation of discrete cortical regions before spreading to the entire cortical mantle and the thalamus.
3. The accepted view of strong burst firing in thalamic relay neurons during typical absence seizures is no longer tenable, since recent experiments in models of this disease under un-drugged conditions clearly show a lack of such type of firing during absence seizures.
4. Contrary the long-held belief of a decreased GABAergic function, recent experiments indicate a clear gain-of-function in all genetic models of typical absence seizures, which results from an abnormality in one of the GABA transporters (GAT-1) that is present in thalamic astrocytes.

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13:15-14:00

**Thalamo-cortical dysrhythmia: diagnostic and therapeutic experience in epilepsy**

D. Jeanmonod, Zurich, Switzerland

Generalized epilepsies have been classically conceptualized as having a subcortical, i.e. thalamic origin. There is less but significant evidence in the literature that focal epilepsies, seen usually as caused by a cortical mechanism, might be due to an overactivity of the recurrent coherent thalamocortical dynamics, as proposed by Llinas and coworkers and named thalamocortical dysrhythmia. Low threshold calcium spike bursts, central in the dysrhythmic process, have indeed been recorded in the medial and mediodorsal/anterior thalamus of patients suffering from focal or multifocal, frontal or parietal epilepsies. We have proof of principle evidence, on a pilot group of patients, for a selective stereotactic medial thalamic and prethalamic control of the epileptic dysrhythmia, confirming earlier experiences.

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14:00-14:30

### **Thalamo-cortical dysrhythmia: theoretical modelling**

H. Proske, Zurich, Switzerland

Functional stereotactic lesions in the central-lateral nucleus of the thalamus (CL) have proved to be an effective treatment of neurogenic pain and other neurological disorders associated with thalamocortical dysrhythmia (TCD). The mechanism underlying the patient's recovery after the surgery are as yet unclear.

We hypothesized that the unique role played by non-specific midline nuclei (like CL) in thalamocortical dysrhythmia is based on divergent intrathalamic connectivity. In order to test this hypothesis we built a spiking computer model of the human thalamocortical system consisting of specific, non-specific and reticular thalamic nuclei. The model aimed to faithfully recreate anatomy and physiology of the thalamus.

In our simulations of the thalamocortical system deafferentation of peripheral thalamic afferents leads to hyperpolarization and subsequent bursting in the reticular nucleus. This provides strong inhibitory feedback to both the specific and non-specific thalamic nuclei and initiates a feedback cycle of thalamic bursts in the alpha frequency range. In the case of thalamocortical dysrhythmia local deafferentation of thalamic areas in interaction with normally functioning areas interfere with the alpha rhythm to produce slower theta oscillations, in accordance with physiological data from TCD patients.

Functional silencing of the non-specific model nucleus limits reverberation and rescues the system from these oscillations. The same effect could be achieved by means of an increased input into the non-specific nucleus from cortical areas.

The model predicts that invasiveness of the functional neurosurgery could potentially be reduced by targeting only deafferented areas in the midline nuclei as these are the key areas for generation and sustain of pathological rhythms in the model.

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14:30-15:00

### **Non-invasive functional neurosurgery using transcranial MR-guided high intensity focused ultrasound**

E. Martin, Zurich, Switzerland

Ernst Martin [1], Daniel Jeanmonod [2], Anne Morel [2], Eyal Zadicario [3], Beat Werner [1]

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Transcranial magnetic resonance (MR)-guided high-intensity focused ultrasound (tcMRgHIFU) implies a novel, non-invasive treatment strategy for various brain diseases.

For over 50 years researchers have been seeking a way to perform noninvasive thermal ablation for brain treatments<sup>1,2</sup>. Recent technical advances have made magnetic resonance (MR)-guided high-intensity focused ultrasound (MRgHIFU) a firmly established modality for noninvasive surgery under closed-loop image guidance and control throughout all steps of the intervention process<sup>3-5</sup>. MR imaging (MRI) allows for precise intraprocedural localization of the ablation target<sup>6</sup>, definition and verification of safety margins for the ultrasound treatment, real-time monitoring of thermal ablation dynamics<sup>7</sup>, and intratreatment and posttreatment assessment of intervention results. Thanks to its noninvasiveness, MRgHIFU minimizes the risk of bleeding and infection and avoids collateral damage to nontargeted tissue<sup>8</sup>. In addition, it does not involve ionizing radiation. Transcranial application of MRgHIFU, therefore, promises to become an important new modality for neurosurgical interventions<sup>9,10</sup> and is envisioned to enable novel treatment strate-

gies against a variety of brain diseases<sup>5,11-13</sup>.

Based on our long-term clinical experience in functional neurosurgery of neuropathic pain with stereotactic interventions in the medial thalamus<sup>14-16</sup>, we developed intervention processes to access ablation targets in the brain noninvasively, using transcranial MRgHIFU (tcMRgHIFU). Following preclinical studies with phantoms, biological tissues and human ex vivo head preparations, a clinical phase I study was initiated to investigate the feasibility, reproducibility, accuracy and safety of tcMRgHIFU for functional neurosurgery. The study was approved by the ethics committee of the University and the State of Zurich.

Ten patients with chronic neuropathic pain scheduled for central lateral thalamotomy (CLT) were enrolled after obtaining fully informed written consent. The treatments were conducted on a clinical prototype system for transcranial MRgHIFU with a phased array of 1024 elements, operating at 650kHz (ExAblate 4000, InSightec, Tirat Carmel Israel) integrated into our clinical 3Tesla MR-system (GE, Milwaukee USA). The stereotactic targets were located using the multiarchitectonic Morel atlas of the human thalamus and basal ganglia<sup>17</sup>. Assessment of ablation dynamics, treatment results and patient outcome were done by MR-imaging, MR-thermometry, stereotactic lesion reconstruction and clinical/neurological patient follow up. All treatments were well tolerated without neurological deficits. Peak focal temperatures ranged from 51°C to 60°C and created precisely located ablations of up to 5mm in diameter in the posterior CL thalamic nucleus of the patients. Being not limited by trajectory restrictions individual treatment planning could fully exploit the ability of TcMRgHIFU to create optimally shaped lesions adapted to the anatomy. The preliminary findings of our ongoing clinical phase I study on nine patients indicate for the first time that tcMRgHIFU is a safe, reliable, and precise modality for noninvasive neurosurgical interventions, and highlight the potential of this novel technology for other applications<sup>3,5,7,13,18</sup>.

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Thursday, September 3, 2009, 12:45–14:15

Chair: D. Prayer, Vienna, Austria

**P01 Diffusion tensor imaging reference values of the subplate in very-low-birth-weight infants**

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### **Aim**

Very-low-birth weight (VLBW) infants are born in a critical period of brain development. In addition they are subject to environmental stimuli that can interfere with normal brain development. Subsequently, long term functional outcome is frequently impaired. Many intervention studies in preterms are aimed to improve long term outcome, but short term proxy outcome measurements are lacking. Subplate development could be such a marker. To provide normal diffusion tensor imaging (DTI) reference values for the subplate of VLBW infants.

### **Methods**

We retrospectively analyzed DTI images of 23 VLBW infants (26–30 weeks gestational age (GA)) without evidence of white-matter injury on conventional MRI sequences, and with normal outcome (Bayley-II scales assessed at age 2 and 5 years). All patients were scanned in the first four days of life. For DTI an echoplanar sequence with diffusion gradient ( $b = 1,000 \text{ s/mm}^2$ ) applied in 25 non-collinear directions was used. We identified the subplate visually on the  $b_0$ -reference image and used single voxel regions of interest placed on predefined regions. We measured fractional anisotropy (FA) and apparent diffusion coefficient (ADC) values in both the frontal and temporal subplate and cortex.

### **Results**

A statistically significant inverse correlation was found between GA and FA of the frontal ( $r = -0,6107$ ,  $p = 0,002$ ) and temporal ( $r = -0,4912$ ,  $p = 0,0327$ ) cortex. ADC values were found to have a significant correlation with GA in the frontal ( $r = 0,4758$ ,  $p = 0,0217$ ) and temporal ( $r = 0,5540$ ,  $p = 0,0138$ ) subplate.

### **Conclusions**

Diffusion tensor imaging allows in vivo exploration of the evolving cortical subplate. So far, however, the clinical use of this technique is restricted by the lack of reference values. We show FA and ADC values of subplate and cortex in VLBW infants with normal developmental outcome, to be used as reference.

### **Acknowledgements**

This study was supported by a grant from the Beatrix Foundation.

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### P02 **Imaging reduced visual print processing in dyslexia: a multi-center fMRI study**

U. Maurer [1], S. Brem [1], M. Kronbichler [2], M. Schurz [2], V. Blau [3], J. Reithler [3], S. van der Mark [1], E. Schulz [1], K. Bucher [1], The Neurodys Consortium [1], E. Martin [1], L. Blomert [3], H. Wimmer [2], D. Brandeis [1]

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#### **Aim**

The visual word form system (VWFS) is thought to be located in the inferior occipito-temporal cortex of the left hemisphere, as this region shows activation during print processing and reduced activation in dyslexia. Contrasting print to control stimuli, such as symbol strings, has revealed a posterior-to-anterior gradient of specialization, but also resulted in less robust reading and dyslexia effects in the small samples used. Here we aim to investigate these effects in a larger, multicenter sample of children and to control or account for variation induced by handedness, age and gender.

#### **Methods**

Across the 3 centers, 154 children (7.8-12.2 years) viewed words and symbol strings while functional MR images were recorded. After excluding subjects with excessive motion and left-handedness, the data of 60 dyslexic and 55 control children were analyzed (SPM5) using a literature-based ROI analysis and a voxel-based whole brain analysis.

#### **Results**

The ROI analysis of the VWFS revealed a left-lateralized tuning gradient in control children, which differed in dyslexic children (hemisphere x condition x roi x dyslexia interaction;  $p < 0.05$ ). The whole brain analysis revealed robust effects of larger activation for words than symbols in inferior frontal and inferior occipito-temporal regions ( $p < 0.05$ , FWE-corrected) and confirmed the dyslexia effects of the ROI analysis: controls showed larger word-symbol differences than dyslexics in inferior occipito-temporal regions ( $p < 0.001$ , cluster-size  $> 20$  voxels), whereas the reverse was found in frontal regions presumably reflecting compensatory activation in dyslexia.

#### **Conclusions**

The inferior occipito-temporal cortex shows a robust specialization for print in a large group of right-handed children. The gradual posterior-to-anterior sensitivity within this VWFS is reduced in dyslexic children. Future analyses will test for modulatory effects of age and gender.

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### P03 MRI pattern recognition in hypomyelinating disorders

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#### Aim

The aim of this study was to determine whether MRI pattern recognition can play a role in distinguishing between different hypomyelinating disorders. This would greatly facilitate diagnostics. In addition, MRI pattern recognition might help to define novel disorders among hypomyelinating disorders of unknown origin.

#### Methods

Patients with a genetic diagnosis of Pelizaeus-Merzbacher disease (PMD)<sup>1</sup> or hypomyelination with congenital cataract (HCC)<sup>2</sup>, a clinical diagnosis of hypomyelination with hypogonadotropic hypogonadism and hypodontia (4H-syndrome)<sup>3,4</sup>, or an MRI diagnosis of hypomyelination with atrophy of the basal ganglia and cerebellum (HABC)<sup>5</sup> were included. MR images of 87 patients were retrospectively reviewed. The investigators scoring the MRIs were blinded for the diagnosis. All images were reviewed according to a previously established scoring list<sup>6</sup>.

#### Results

Patients were grouped according to their pattern of abnormalities on MR images. Most patients were grouped with patients with the same disease, although some diseases were divided into two or three categories. Some patients did not fall into a specific group. No mixing of diseases occurred. MR images of HABC patients showed a variable degree of hypomyelination, early disappearance of the putamen and early atrophy of the cerebellum. In PMD, supratentorial myelination was arrested at an early age with homogeneous hypomyelination without any spatial variation. Patients with HCC had hypomyelination with additional more prominent signal abnormalities in the central and periventricular white matter. In 4H-syndrome, patients had somewhat more myelin, corresponding with the pattern of normal myelination at around 6 months. Cerebellar atrophy was early.

#### Conclusions

HABC, HCC, PMD, and 4H-syndrome can be distinguished on the basis of their patterns of MRI abnormalities. Important items are: degree of the hypomyelination, presence of areas of more prominent signal abnormalities, early cerebellar atrophy, and basal ganglia abnormalities.

#### Acknowledgements

We would like to thank many colleagues for sending the MRIs for review.

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### P04 Multimodal presurgical evaluation of pediatric epilepsies: the role of language fMRI

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#### Aim

fMRI is a reliable and non-invasive method to monitor language representation. The technique is increasingly used in the clinical (pre-surgical) setting also in children. Here, we report on the usefulness of language fMRI in the context of multimodal presurgical evaluation of pediatric epilepsies and its validity in comparison with invasive procedures and postoperative language abilities.

#### Methods

Ten patients with pharmaco-refractory focal epilepsies (age range 7 to 26 years) underwent language fMRI (1.5 T, block design, silent generation of word chains<sup>1</sup>, listening to "beep stories"<sup>2</sup>). A Wada (intracarotid Amytal) test has already been performed in 2 patients and is planned in 2 patients. In 4 patients, it was not considered feasible and not necessary in 2 patients. One patient has already been operated (see below).

#### Results

fMRI was successfully performed in 9/10 patients. Atypical (right or bilateral) language lateralization was found in 3/9 patients. A Wada test (performed in 2 patients) was unsuccessful in one patient (initial sedation, fast recovery from hemiparesis). The one successful Wada test showed left dominance, concordant with fMRI. One patient with right-hemispheric fMRI activation during language perception (in whom Wada testing was not feasible due to low compliance) underwent an anterior and posterior disconnection with preservation of sensorimotor cortex. Her language abilities were unchanged postoperatively.

#### Conclusions

fMRI can provide useful information in the presurgical evaluation of pediatric epilepsies, even in cases with insufficient compliance for Wada testing. We could confirm its validity in two patients as yet: in one case (typical language lateralization) with the Wada test, and in a second case (atypical language representation) with preserved post-operative speech after extensive left-hemispheric disconnection.

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### P05 Outcome of severe unilateral cerebellar hypoplasia

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#### Aim

Complete or subtotal absence of one cerebellar hemisphere is exceptional, only single cases have been described. Therefore, we aimed to assess the long-term outcome in children with severe unilateral cerebellar hypoplasia (UCH).

#### Methods

As part of a retrospective study we report 8 patients with UCH and describe neuroimaging features, clinical findings, and cognitive outcomes.

#### Results

Of the eight cases, two patients had an abnormal prenatal MRI at 21 weeks of gestation and in one case the pregnancy was terminated. The left cerebellar hemisphere was affected in 6 cases, the right in 2. The vermis was involved in 5 cases and a contralateral brainstem asymmetry was present in 6 patients. The volume of the posterior fossa was reduced ipsilateral to the cerebellar hypoplasia in 4, normal in 3, and enlarged in one case. The mean age of the patients at the last follow-up was 7 years 3 months (range 2 years 3 months to 14 years 11 months). Neurological findings included truncal ataxia and muscular hypotonia in 5 patients, limb ataxia in 3, and head nodding in 2. Three patients experienced cognitive impairment requiring special educational provision. Five patients had speech and language disorders and one patient a severe behavioural disorder.

#### Interpretation

Severe unilateral cerebellar hypoplasia represents a residual change following a disruptive prenatal cerebellar insult, most likely haemorrhagic. The outcome in these children is variable, ranging from almost normal development to marked developmental impairment, whereas truncal and limb ataxia were not leading signs. It seems that involvement of the cerebellar vermis is associated with a poorer cognitive outcome, but a strict anatomical and functional correlation could not be established.

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### P06 Periventricular nodular heterotopia and limb reduction defects: an expanding spectrum

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Malformations of cerebral cortical development, in particular periventricular nodular heterotopia (PNH) and limb reduction defects are reported as associated congenital anomalies in the literature. Patients with PNH and limb defects can be classified as having syndromes such as amniotic band sequence or Adams-Oliver. For these syndromes causes are unknown, and both environmental and genetic factors have been implicated. Controversy exists whether these should be considered separate entities. We present three patients with PNH and limb reduction defects to support the hypothesis that these should be considered to be part of one spectrum of disease, and highlight the variable severity of the clinical and neuroradiological phenotype. Chromosomal abnormalities were excluded by copy number analysis on 250K SNP microarray data. In the most severely affected patient homozygous areas suggest parental consanguinity.

Both research done on reduction defects as on PNH caused by mutations in well-known genes, suggest the involvement of vascular developmental pathways. The combination of limb reduction defects and PNH is likely to have a common causative mechanism. Recognition and grouping of patients with abnormalities in this spectrum will help elucidating the cause.

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### P07 Restricted diffusion in inflammatory lesions in children

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#### Aim

Diffusion-weighted imaging (DWI) has a well-established role in the assessment of acute ischaemic infarction in adults and children demonstrating the characteristic cytotoxic oedema. On the other hand, the wide application of this technique during the last decade has widened the spectrum of central nervous system disorders associated with restricted diffusion, including inflammatory and demyelinating disorders<sup>1,2</sup>.

#### Methods

We report a small series of four children (3 females, mean age 6 years, range 2,5-10 years) with different types of inflammatory lesions showing only restricted diffusion at presentation.

#### Results

Two patients presented with clinically mild encephalitis/encephalopathy and callosal and hemispheric white matter lesions with reversible restricted diffusion following a short viral illness ("extended MERS"<sup>3,4</sup>). The third patient was diagnosed an acute disseminated encephalopathy (ADEM) and presented with bilateral asymmetric periventricular and subcortical white matter abnormalities with marked restricted diffusion throughout the lesions. The last patient presented with an acute onset of left 3rd nerve palsy, diplopia, right upper motor neurone facial palsy, mild right hemiparesis and ataxia. The MRI scan showed a unilateral midbrain lesion with restricted diffusion. Vascular imaging was normal, neurological recovery was rapid and the lesion was thought to be inflammatory in origin.

#### Conclusions

Restricted diffusion is not confined to acute ischaemic infarction. Inflammatory and demyelinating lesions demonstrate decreased diffusivity on DWI and may be reversible and associated with a benign clinical course.

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### P08 Restricted proton diffusion found in vanishing white matter disease

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#### **Aim**

Although vanishing white matter disease (VWM) is one of the most prevalent inherited leucoencephalopathies, the pathomechanisms surrounding the brain lesions are largely unclear. Especially, cytotoxic edema associated active demyelination was rarely found in VWM. Therefore we performed this study.

#### **Methods**

Four patients with genetically proven VWM underwent MR examinations including diffusion weighted imaging. The imaging data were analyzed qualitatively and quantitatively with attention being paid to find an indication of active demyelination.

#### **Results**

Besides typical brain lesions with diffuse white matter changes and myelin loss, restricted proton diffusion – interpreted as cytotoxic myelin edema – was for the first time found in scarce remaining white matter of two of the patients.

#### **Conclusions**

The present observations may expand the spectrum of MRI features of VWM. The knowledge that cytotoxic edema associated active demyelination can be evident in VWM, even in cases with advanced loss of myelin, may contribute to the understanding of the pathomechanism.

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### P09 Serial qualitative and quantitative MR imaging in term infant after postnatal collapse

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#### Aim

(i) To assess the evolutionary change in serial conventional and quantitative T2 and ADC MRI in a term infant with postnatal collapse

(ii) To compare these findings with one age-matched MRI from 9 apparently healthy term infants.

#### Methods

Term infant (GA at birth 38 weeks) underwent MRI at 12, 33 and 88 hours after postnatal collapse which had occurred at one week of age. Nine control infants (mean (SD) GA at birth 38.3 (1.2) weeks) were scanned at mean age 39.8 (1.6) weeks.

MRI data was acquired on 1.5T scanner including T1 weighted (T1w), T2 weighted (T2w) fast SE, T2 relaxometry and diffusion weighted imaging (DWI). ROIs of predefined size were drawn. A pediatric neuroradiologist visually assessed the conventional images.

#### Results

Imaging at 12 hours

Visual assessment showed bilateral oedema of thalami and PLIC. T2 was prolonged in caudate nuclei (182 ms), thalami (202 ms) and brainstem (182 ms) compared to controls (mean (SD)) (141 (11), 161(12), 140(13) ms respectively). ADC was decreased in thalami ( $0.86 \times 10^{-3} \text{ mm}^2/\text{s}$ ) and in cerebral hemisphere white matter (WM) ( $1.34 \times 10^{-3} \text{ mm}^2/\text{s}$ ) compared to controls (1.04 (0.05), 1.47 (0.07)  $\times 10^{-3} \text{ mm}^2/\text{s}$  respectively).

Imaging at 33 hours

Additionally, visual assessment showed involvement of putamina and cerebral hemisphere WM. T2 was prolonged in putamina (168 ms) compared to controls (141 ms (7)). Globus pallidi (GP) ADC ( $0.94 \times 10^{-3} \text{ mm}^2/\text{s}$ ) was lower compared to controls (1.11 (0.04)  $\times 10^{-3} \text{ mm}^2/\text{s}$ ).

Imaging at 88 hours

Visual assessment showed diffuse cerebral swelling, abnormal SI in cortex, cerebral WM, DGM structures, brainstem and cerebellum. T2 increased further in thalami, DGM and brainstem. ADC decreased further in cerebral WM, thalami and DGM.

#### Conclusions

Quantitative MR detected more involved regions at 12 and 33 hours than conventional imaging where the full extent of injury was seen at 88 hours of age. These findings support the use of quantitative T2 and ADC in early brain MRI for neonatal encephalopathy.

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### P10 Changes in deep sleep and local grey matter volumes during development

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#### Aim

Extensive maturational changes take place in the human brain during adolescence. Anatomically, such maturation can be assessed in vivo on MR images as changes in grey matter volumes<sup>1</sup>. In parallel, the sleep EEG reveals prominent changes of activity in the slow-wave frequency range, the major characteristic of deep sleep<sup>2,3</sup>. Based on the hypothesis that sleep slow waves actively support developmental processes in the young brain, we looked for grey matter correlates of EEG slow wave activity (SWA; power between 1–4.5 Hz) in the brain.

#### Methods

In a sample of 21 children (13 boys; age range 9–18 years, mean=13.6 y, SD=3.1 y) we correlated local grey matter volumes with SWA (mean of two nights; all-night high density EEG was recorded using Geodesics Sensor Nets composed of 128 electrodes) using the SPM5 software (<http://www.fil.ion.ucl.ac.uk/spm>). Grey matter segments were smoothed with an 8mm Gaussian kernel and compared voxel by voxel using voxel-based morphometry<sup>4</sup>. These correlation maps were overlaid with maps of the grey matter decrease with age.

#### Results

We found significant positive correlations between SWA and grey matter predominantly in areas of the medial and lateral parietal region, the precuneus and the ventromedial prefrontal cortex. These areas with positive correlations generally aligned with areas showing a decrease of grey matter during childhood. The few areas showing a negative correlation between grey matter and SWA did not show a relationship to age dependent decreases in grey matter.

#### Conclusions

Our preliminary data show that the decrease of sleep SWA during adolescence is largest in regions with a significant decrease in grey matter volume. Our findings support a close relationship between brain activity during deep sleep and maturation-related cortical plasticity.

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#### Acknowledgements

This work was supported by the SNF Professorship Grant PPO0A-114923 and a research grant of the Children's Hospital Zurich

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### P11 Volume of unmyelinated white matter predicts outcome in premature born neonates

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#### Aim

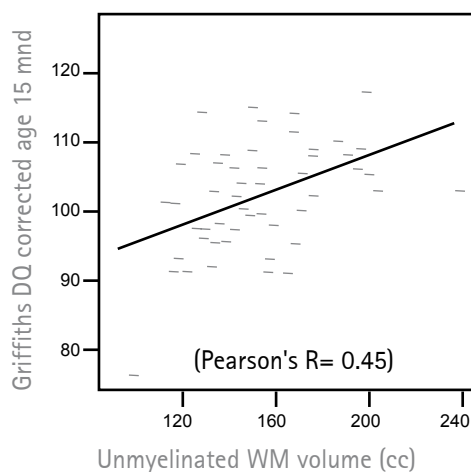
The aim of this study was to assess the unmyelinated WM (UWM) volume using a newly developed automatic probabilistic segmentation method and to evaluate whether the UWM volume predicts neurodevelopmental outcome in premature born babies at the corrected age of 15 months.

#### Methods

Neonates born at a gestational age (GA) below 31 weeks who reached term equivalent age (TEA) in 2007 were enrolled in a large prospective study. Up to date sixty neonates have been analyzed. Their mean GA was 28.9 weeks (range 25,0-30,9 weeks) and their mean birth weight was 1129 g (630-1910 g). On a 3.0-T whole-body system cranial MRI was acquired around TEA, including 3D T1- and T2-weighted images. A newly developed automatic probabilistic segmentation method, based on the KNN-classification method in<sup>1</sup>, was used for segmentation of the UWM, the total brain volume (TBV) and the total intracranial volume (ICV). Neurodevelopmental outcome was evaluated using the Griffiths' developmental assessment scale at the corrected age of 15 months. The relation between the Griffiths' DQ and the UWM volume was assessed. To correct for brain size, these analyses were repeated for the ratio UWM/TBV and DQ.

#### Results

The mean UWM in our cohort was 154 cc, mean TBV 382 cc and mean total ICV 476 cc. There was a positive correlation between the UWM volume at TEA and the DQ on the Griffiths score. After correction for GA, gender and postmenstrual age (PMA) the relation remained statistically significant (Pearson's R=0.55). We found a positive correlation between the ratio UWM/TBV and DQ as well (Pearson's R=0.46, after correction for GA, gender and PMA: Pearson's R=0.57).



#### Conclusions

UWM volume predicts the neurodevelopmental outcome of premature born neonates at the corrected age of 15 months. A relatively larger UWM volume compared to total TBV was the best predictor for neurodevelopmental outcome.

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## Abstracts of Postersession 2

Thursday, September 3, 2009, 12:45–14:15

Chair: E. Widjaja, Toronto, CA

### P12 A DTI tractography and TBSS study of young children with autism

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#### Aim

The objective of this study was to examine white matter integrity in young children with autism using advanced DTI analyses.

#### Methods

Subjects with autism (AUT, n=19 age:  $2.98 \pm 1.19$ ) and typically developing control subjects (TD, n=23, age:  $3.40 \pm 1.47$ ) were included in this study. Tractography analysis was applied to extract three major fiber bundles: the corpus callosum, the cortico-spinal tract (CST) and the superior longitudinal fasciculus (SLF). Further segmentation of the corpus callosum (CC) was conducted according to the Witelson method. Mean diffusivity, FA, axial and radial diffusivities were calculated for each fiber segment and were compared between the groups. Tract Based Spatial Statistics (TBSS) was used to compare the diffusivities values between groups in the entire white matter skeleton.

#### Results

Lower radial and axial diffusivity and higher FA were found in the body of CC (Witelson II, III and IV) of the autism group, whereas, higher radial diffusivity, axial diffusivity and ADC values were found in the left SLF yet not in the right. No between groups difference were detected in the CST fibers. In the TBSS analysis, significant increase in FA in the midbody of the CC was detected in AUT compared to TD.

#### Conclusions

A decline of the structural coherence of white matter, as was shown in this study, can influence connectivity between different brain regions and may cause some of the cognitive and social symptoms seen in autism.

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### P13 Application of Tract-Based Spatial Statistics in a cohort of extremely preterm infants

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#### **Aim**

To explore Tract-Based Spatial Statistics (TBSS) for analysis of MR diffusion data (DWI) at term equivalent age. TBSS is a whole-brain, observer-independent tool for voxel-wise statistics for multi-subject comparison of diffusion parameters. Few studies have applied TBSS to neonatal data.

#### **Methods**

We acquired DWI data at term equivalent age in 180 extremely preterm infants (EPT; born at < 27 weeks' gestation, mean gestational age 25w4d (SD 1w) and in 21 healthy term-born controls on a 1.5 T system: spin-echo EPI sequence (TE/TR=74/7000 ms; voxel size=1.4x1.4x2.2 mm<sup>3</sup>), 15 directions (b=700 s/mm<sup>2</sup>), one b=0 image. The TBSS processing protocol was modified for neonatal data. 95 good quality data sets were analysed (n=81 preterms, n=14 controls). Fractional anisotropy (FA) maps were compared between (1) EPT and controls, (2) within the EPT group between those with normal MRI on visual inspection and those with diffuse high signal intensity (DEHSI).

#### **Results**

Our modified protocol resulted in satisfactory co-registration of FA maps and a good quality skeletonised mean FA image. Analyses (1) and (2) indicated FA differences in the body and splenium of the corpus callosum. This is consistent with findings from an ROI analysis in the same cohort. In contrast to the previous ROI analyses, TBSS analysis, however, did not reach significance (p=0.3) and did not replicate FA differences in the centrum semiovale and posterior limb of the internal capsule.

#### **Conclusions**

TBSS is applicable to neonatal data, but requires modification of the processing protocol. Cautious interpretation of the findings is required.

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### P14 Diffusion tensor imaging and tractography in children with congenital hemiparesis

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#### **Aim**

Diffusion tensor imaging (DTI) and tractography are a MR technique that allows "in vivo" evaluation of white matter fibers, namely of the pyramidal tract. The aim of this work is to present cases of children with congenital hemiparesis and evaluate the cortico-spinal tract on DTI and tractography.

#### **Methods**

14 cases of patients with congenital hemiparesis were evaluated by MRI, with T1 and T2 sequences, DTI and 3D reconstruction tractography. Analysis of DTI/tractography was made.

#### **Results**

MRI demonstrated as causes of hemiparesis strokes and malformations of cortical development, but there was also cases with no alteration on T1 and T2 anatomical images or with alterations in places where it was not presumed pyramidal tract involvement. In all children alterations were found on DTI/tractography, with reduction of the cortico-spinal tract related to the neurological deficit (contralateral to the hemiparesis), including in the patients with no other alterations.

#### **Conclusions**

Evaluation by DTI/tractography is an important and useful tool in the study of children with congenital hemiparesis, including those with a normal MRI (on anatomical T1 and T2 images). It is a method with a large potential in the pediatric field and with emerging applications, not only in tumoral and destructive pathology but also in congenital malformations and developmental disorders.

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### P15 Functional MRI of the language domain in 2 children with epilepsy: two tasks is better than one

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#### Introduction

Functional MRI has been used increasingly to determine hemispheric dominance for language (Stippich et al., 2007), also in children (Kesavadas et al., 2007). We here report on our experience of performing clinically-indicated functional MRI in 2 children with epilepsy where only the combined analysis of two tasks revealed the full extent of language reorganization.

#### Subjects and methods

A 5-year-old, left-handed girl with tuberous sclerosis was seen for intractable seizures thought to originate from a left inferior-frontal tuber. A 17-year-old boy with daily seizures due to a left-frontal focal cortical dysplasia was also referred for scanning. Both children were scanned on a 1.5T Siemens Sonata scanner (Siemens Medizintechnik, Erlangen, Germany). We used two different fMRI tasks to investigate language lateralization (Wilke et al., 2005, 2006) in the frontal and in the temporal lobe. Data processing was done in SPM5 (UCL London, UK), running in Matlab (Mathworks, Natick, MA, USA). Lateralization was assessed by calculating a weighted lateralization index (Wilke & Schmithorst, 2006) in the frontal and the temporal lobe.

#### Results

In the first case, right-dominant frontal activation was seen in one task and right-dominant temporal activation was seen in another task. Only jointly analyzing both tasks showed the completely shifted whole language network. In the second case, the first task showed left inferior-frontal activation in one task, but right inferior-frontal activation was seen in another task, suggesting hemispheric dissociation of language functions.

#### Conclusions

Clinically-indicated functional MRI of the language domain is feasible in children with epilepsy, and provides important information. In both cases, the full extent of reorganization was only seen when analyzing two different MRI tasks, underscoring the recommendation to use a task panel whenever possible (Gaillard et al., 2004).

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### P16 Hand function and cortical thickness in very low birth weight adolescents

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#### Background

Abnormal cerebral MRI findings as well as poor fine motor function have been reported in very low birth weight (VLBW) populations. Also, higher prevalence of left-handedness has been reported in VLBW children.

#### Objective

To study if thinning of motor cortex is associated with reduced fine motor function and unclear hand preference in VLBW adolescents.

#### Material and methods

At 14 years of age, 40 VLBW adolescents with birth weight below 1501 g and 50 term controls with normal birth weight were assessed by the manual dexterity subscore of the Movement Assessment Battery for Children, the motor coordination supplementary test of the Visual-Motor Integration test and the Edinburgh Handedness Inventory. An automated MRI technique at 1.5T for morphometric analyses of cortical thickness was performed. Poor fine motor function was defined as a manual dexterity score below the 15th centile in the control group. Correlations between cortical thickness and manual dexterity score, motor coordination score and laterality index were evaluated by a general linear model applying a 'false discovery rate' to the region of interest (the precentral gyrus).

#### Results

In VLBW adolescents with poor fine motor function, poorer manual dexterity and motor coordination scores were related to thinner cortex in the hand area of the precentral gyrus in the left hemisphere ( $p < 0.0001$ ). The same area was thinner in adolescents with low laterality index ( $p < 0.0001$ ). Among VLBW adolescents with normal fine motor function and in controls no such association was found.

#### Conclusions

We found a correlation between motor cortical thinning and clinical test results in VLBW adolescents with poor fine motor function. We speculate that ante-/perinatal brain damage affecting motor cortex in VLBW children have clinical consequences resulting in unclear hand preference and reduced fine motor function.

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### P17 Prenatal nystagmus

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#### **Purpose**

To evaluate whether fetal nystagmus and other types of fetal eye movements can be demonstrated using dynamic MR sequences.

#### **Patients and methods**

In 50 fetuses aged from 18-40 gestational weeks (GW) with presumed normal brain development (defined by clinical history and normal brain maturation on MR images), eye movements were studied during MR examinations. Fetal MRI was done for clinical purposes on a 1.5T system using a sense cardiac coil. Dynamic steady-state free precession sequences (slice thickness 15-20 mm) with 6 frames/second, and subsequent calculation for real-time appearance, were acquired 2-5 times in axial and/or coronal plane for 35 seconds. Fetuses were divided into groups: GW 18-23 (12 cases), 24-32 (22 cases), and 33-40 (16 cases).

Eye-movements were assessed following the classification of Birnholz (Birnholz, J.C. The development of human fetal eye movement patterns. *Science*. 1981, 213:679-81.) into: short linear deviation of the bulbs to the periphery (type I), prolonged deviation of the bulbs (type II), a deviation with a rotatory component (type III) and nystagmoid movements (type IV). No eye movements during the observation time were classified as type 0.

#### **Results**

Nystagmoid eye movements (type IV) were only observed after GW 23.

Between GW 33 and 40 1 fetus displayed type I movements, 6 fetuses displayed type II movements, type III movements were observed in 5, type IV movements in 4 fetuses, with a combination of type I or II and type III or IV patterns in 4 fetuses. 5 Fetuses displayed type 0 movements.

In GW 24-32 type I movements were seen in 6, type II in 7, type III in 6, type IV in 1, Type 0 was seen in 7 fetuses. Combinations of type I or II with type III movements occurred in 5 cases.

In fetuses from GW 18-23 only type I (5) and type 0 movements (7) occurred. In this group no nystagmoid movements (type IV), type III or type II movements were observed.

#### **Conclusions**

The development of fetal eye movements can be recorded in-vivo using dynamic MR sequences. Age-related eye movement patterns can be recognized, reflecting maturational changes in the brainstem. Prenatal nystagmoid movements were only observed in fetuses older than 23 GW.

In the future the assessment of fetal eye movement patterns may be helpful in the prognosis of malformations associated with impairment of brainstem functions, such as, for instance, molar-tooth malformations or hydrocephalus.

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### P18 T1 weighted MRI of the fetal brain using single shot techniques

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#### **Aim**

T2-weighted single-shot fast spin-echo (ssFSE) sequences dominate fetal brain MRI protocols. ssFSE allows high quality, rapid acquisition<sup>1</sup> which is virtually insensitive to the unpredictable motion of the fetal brain in utero. Commonly employed T1-weighted sequences including fast field echo (FFE)<sup>2</sup> and spoiled FFE<sup>3</sup> prove less successful. The aim of this study was to explore single-shot methods for T1-weighted imaging using inversion recovery (IR) methods, ideally with option to produce 3D reconstructed images.

#### **Methods**

8 adult volunteers and 21 fetal patients (median 26/40, range 20.4/40 - 37.3/40) were scanned on a Philips 1.5T MRI system using the cardiac phased-array coil. Different IR ssFSE parameters were explored, including echo time (TE), inversion time (TI), inter-echo spacing and k-space echo encoding order for ssFSE and type of reconstruction (real versus magnitude). Parameters improving image quality were incorporated in a final protocol and compared to the standard T1 breath hold FFE protocol. Snapshot to Volume Reconstruction (SVR)<sup>4</sup> was applied to the T1-weighted single-shot images.

#### **Results**

A TI of 400ms achieved T1-weighted contrast while being robust to fetal motion between inversion and readout. A TE of ~9.5 ms minimised T2 weighting. Resolution of 1.5 mm<sup>2</sup> x 2.5 mm with Sense factor of 2 allowed fine anatomical detail of the full brain to be observed in ~2 min whilst preserving SNR. At longer TI, brain and cerebrospinal fluid signals can have opposite signs so real reconstruction is optimal, but less robust than magnitude reconstruction. For the selected TI, all signals remain negative so magnitude reconstruction was used with inverted grey scale. Anatomical detail was well reconstructed in 3D by SVR.

#### **Conclusions**

IR prepared ssFSE provides robust T1-weighted images suitable for clinical and research applications. When combined with SVR, high resolution 3D images can be produced. This technique holds promise for advancing T1-weighted imaging in a predominantly T2 weighted field.

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### P20 Imaging the reorganisation of white matter after ischemic stroke in childhood

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#### **Aim**

There is a longstanding discussion in contemporary neuroscience as to what extent injuries in specific areas may impact other brain regions and how far lesions cause alternations of white matter tracts. Moreover, the time lapse of structural changes is largely unknown. As white matter growth is essential for development, the aim of this study is to keep objective records of individual reorganisation processes taking place during sensitive periods after ischemic stroke.

#### **Methods**

Four children underwent Diffusion Q-Ball imaging (QBI) examination three times within one year post-stroke. The examinations on a TIM-Trio 3.0T scanner took place one month, three months and one year after the arterial ischemic stroke occurred. The diffusion sequence is a twice-refocused balanced echo planar sequence used along with house-internal modifications concerning the number and distribution of the calculated gradient directions. Generalized fractional anisotropy as well as ADC maps were calculated.

#### **Results**

The comparison of intra-individual data of the different time slots showed axonal changes over time. Structural reorganization processes have been detected near the lesions as well as far-off the initial lesion site. Variances in the distribution of the axonal fibers have been observed in homotopic areas of the injured tissue as well as in ipsilaterally functionally connected areas. Furthermore, the analysis showed that even very small lesions may trigger extensive reorganization processes of white matter tracts.

#### **Conclusions**

QBI provides a unique insight into the dimensions of neuroplasticity after stroke. Its non-invasive character allows individual analysis to the extent of alternations of white matter tracts over time. Moreover, QBI provides an instrument to assess the severity of ischemic brain insult. In the future this method may also help to evaluate therapeutic interventions and may provide another benchmark for the effectiveness of rehabilitation after stroke.

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### P21 Proton magnetic resonance spectroscopic imaging in pediatric low-grade gliomas

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#### Aim

To investigate whether in vivo proton magnetic resonance spectroscopic imaging (MRS), using absolute measures of total choline (tCho) and total creatine (tCr), can differentiate between pilocytic astrocytoma (WHO grade I) and diffuse, fibrillary astrocytoma (WHO grade II) in children.

#### Methods

Seventeen children (12 children with pilocytic astrocytomas-PA- and 5 children with diffuse, fibrillary astrocytoma-DA-) with astrocytomas were evaluated retrospectively. MRS was performed before surgery or biopsy in all patients with histologically proven low grade astrocytomas. Metabolite concentrations of tCho and tCr were normalized to contra lateral brain tissue. Spectroscopic data was used for statistical evaluation.

#### Results

There was a strong trend ( $P=0.07$ ) towards higher values of tCr in the pediatric DA group. Total choline (tCho) levels did not show any statistical significant difference between the 2 groups. Three out of 5 children with DA showed lactate resonance and only one out of 12 children with PA.

#### Conclusions

Our study shows a strong trend toward higher normalized tCr in children with DA, compared with those with PA. Choline as a single parameter is not reliable in the differential diagnosis of low grade tumors in children. Total Cr normalized concentrations combined with lactate seems to be helpful in the differential diagnosis of PA and DA in children.

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### P22 Spectroscopy in children and adults with pilocytic astrocytomas

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#### Aim

Using MR spectroscopy, we assessed whether choline-containing compounds (tCho), classically related to cell proliferation, were also increased in pilocytic astrocytomas (PA).

#### Methods

Seventeen patients (5 adults, age 20–55 y and 12 children, age 6 mo–15 y) with histologically proven PA were evaluated retrospectively. MR spectroscopy was performed prior to surgery or biopsy in all patients. Signal intensities of tCho and total creatine (tCr) signals were normalized to contralateral brain tissue and statistically evaluated for group differences between adults and children.

#### Results

The tCho levels in our patients were variable with a trend to elevated values, especially in the adult group. tCho levels ranged from 0.86 to 2.92 in the paediatric group (mean: 1.10) and from 1.10 to 5.25 in the adult group (mean: 1.40). Diminished or normal tCr values were observed in all patients.

#### Conclusions

The well known positive correlation between increase of tCho and the grade of gliomas seems to be violated by WHO grade I pilocytic astrocytomas showing a wide range of tCho values with an even marked increase in some cases. No differences have been identified in the MR spectroscopy metabolite profiles between paediatric and adult PA.

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Chair: I. Scheer, Zurich, Switzerland

### P23 Diffusion MRI in the cortico–spinal tract and hand motor outcome in children with unilateral cerebral palsy (CP)

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#### Introduction

In unilateral CP, exact relationships between brain lesions assessed on visual inspection of magnetic resonance (MR) images and outcome are still unclear. Recent studies indicate that diffusion MRI improves detection of brain abnormalities that underly CP<sup>1,2</sup>. Relationships between MR diffusion parameters in the corticospinal tract (CST) and hand motor function are largely unexplored. The objective of this study is to investigate these relationships.

#### Methods

15 children with unilateral CP, mean age 147 (SD 32.2) months, 9 female. 24 controls, mean age 153 (SD 28.2) months, 15 female. Hand function was assessed with the Box&Blocks test.

Axial and coronal T2w, 3D T1w, and diffusion data (SS-EPI sequence:  $b=1000$  s/mm<sup>2</sup>, 45 directions; 6  $b=0$ ; TR/TE=10000/76 ms; FOV=220 mm, 64 slices, isotropic voxels 2.3 mm<sup>3</sup>) were collected on a 1.5T MR system. Data were processed and analysed in FSL 4.1.2. ([www.fmrib.ox.ac.uk/fsl](http://www.fmrib.ox.ac.uk/fsl)). Fractional anisotropy, FA; mean diffusivity, MD; tensor eigenvalues were measured bilaterally in two anatomically delineated regions of interest (ROIs; level of cerebral peduncle and internal capsule). Fiber tracking of the CST was performed bilaterally; asymmetry indices were calculated.

#### Results

Lesions on visual inspection of MRI ranged from white matter damage of immaturity (WMDI) to cortical grey matter injury. In children with CP, FA in both ROIs and over the tract corresponding to the affected hand was lower and asymmetry indices were higher compared to controls. Hand function correlated with mean FA in the CST contralateral to the affected hand. Subjects with WMDI (n=10) showed changes in FA, MD and eigenvalues consistent with what could be expected in (anterograde) Wallerian degeneration<sup>3</sup>.

#### Conclusions

FA measured in the CST appears to be a sensitive indicator of damage to the motor system. It correlates well with outcome. Combined analysis of FA, MD and tensor eigenvalues gives additional insight into changes in tissue microstructure in CP.

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**P24 Early gestational age at birth is associated with white matter microstructural abnormalities that persist into early childhood**

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### **Aim**

The aim of this study was to assess fractional anisotropy (FA) in the white matter of children who were born preterm to test the hypothesis "immaturity at birth is associated with diminished white matter integrity that persists into early childhood".

### **Methods**

47 children who were born preterm (median [range] GA at birth = 29 [24-34] weeks) underwent magnetic resonance imaging (MRI) at 2 years of age (median corrected age at scan = 26 [24-28] months). Infants with focal lesions on imaging were excluded from this study. Diffusion tensor imaging (DTI) was obtained in 15 non-collinear directions and FA maps were generated using fsl ([www.fmrib.ox.ac.uk/fsl](http://www.fmrib.ox.ac.uk/fsl)). Voxel-wise statistical analysis of the FA data was carried out using tract based spatial statistics (TBSS)<sup>1</sup>. The relationship between FA and GA at birth, corrected for age at scan, was assessed using linear regression analysis of voxel-wise cross-subject statistics corrected for multiple comparisons using threshold free cluster enhancement.

### **Results**

A linear relationship between GA at birth and FA ( $p < 0.01$ ) was observed throughout the white matter including the corpus callosum, centrum semi-ovale, cingulum, posterior limb of the internal capsule, fornix and posterior parietal white matter.

### **Conclusions**

We have previously shown that younger gestational age at birth is associated with lower FA values in the white matter in preterm infants at term equivalent age<sup>2</sup>. This study shows that this relationship persists into early childhood and suggests that early impairments in white matter integrity associated with extreme prematurity are not merely delays in maturation that are ameliorated following discharge from the neonatal intensive care unit. Rather these data imply this gestational dependent reduction in FA values, in the absence of major focal white matter lesions, represents enduring oligodendrocyte/axonal abnormalities.

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**P25 Effect of long-term outcome after perinatal asphyxia on cerebral volume in relation to memory function using voxel based morphometry**

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### **Background**

Neonatal encephalopathy (NE) following perinatal asphyxia is considered to be an important cause of later neurodevelopmental disabilities in the term infant. Many of these children experience difficulties when they have to master complex abilities at school age. Recently it has been described that NE has a specific, gradual effect on memory functions.

### **Aim**

To evaluate the effect of NE on (regional) brain structural changes using brain imaging segmentation techniques combined with voxel-based morphometry.

### **Design and methods**

We included 25 children with mild (NE1), 25 with moderate (NE2) perinatal asphyxia, and 50 controls (CTRL). Children were assessed on general intellectual abilities (short-form WISC), verbal memory (WISC subtest digit span forward), visuo-spatial memory (short-term: Kaufman ABC subtest spatial memory; long-term: Rey Visual Design Learning Test (RVDLT) and verbal associative learning (RAKIT subtest learning names). A 3D-volumetric MRI was obtained at 9-10 yrs of age. Brain tissue segmentation was performed to measure absolute volumes of gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF). A voxel based morphometry approach was used to detect volume differences between the groups (with uncorrected  $p$  values of 0.001). All analyses were corrected for age and gender.

### **Results**

A trend was found for reduced GM in the NE2 infants compared to CTRL (774+88 vs. 808+74 ml;  $p=0.08$ ). VBM analysis revealed loss of WM volume in NE patients in the posterior part of the corpus callosum and fornix and GM loss in the occipital lobes compared to CTRL. Significant correlations were found between IQ ( $R$  0.55,  $p<0.001$ ), verbal (Digital span forward;  $R$  0.35,  $p<0.02$ ) and visuo-spatial short-term and long term memory (subtest special memory Kaufman ABC spatial ( $R$  0.43  $p<0.01$ ), RVDLT  $R$  0.31,  $p<0.05$ ) and verbal associative learning (RAKIT  $R$  0.29  $p<0.05$ ) with GM volume. VBM identified volume loss in frontal cortical and subcortical regions to correlate with IQ.

### **Conclusions**

NE tends to decrease total GM volume and affects the WM in the posterior part of the corpus callosum. There seems to be an association between reduced GM volume and poor memory and learning capacities in children with perinatal asphyxia.

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### P26 Intracerebral hemorrhage in fetal MRI

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#### **Aim**

Prenatal appearance and postnatal outcome of fetal intracerebral hemorrhage (ICH) detected by in-vivo MRI.

#### **Methods**

23 fetuses aged from 18–39 gestational weeks who underwent fetal MRI were included. MRI was performed using a 1.5T superconducting system, and a sense cardiac coil. Ultrafast T2-weighted fast spin-echo sequences, T1-weighted gradient-echo sequences, diffusion-weighted sequences, and echoplanar sequences were performed with a slice-thickness of 3–5 mm, in 3 orthogonal section planes. Evaluation included identification of blood-breakdown products (BBP), associated changes, such as brain-edema and/or widening of ventricles, and/or tissue loss. Classification of intraventricular hemorrhage (IVH) was done following the Burstein criteria (Grade I–IV). For follow-up, postnatal imaging studies and/or clinical assessment was available in 11 cases.

#### **Results**

BBP were identified in 13 cases within the ventricles and/or in the ependyma and in 8 fetuses within the parenchyma. In 2 cases no BBP were detected, but associated findings suggested the former presence of ICH. These changes consisted of: ventricular enlargement, tissue loss and brain-edema. In 3 cases the pregnancy was terminated, 3 fetuses died intrauterine, 11 were born alive (1 Grade I, 2 Grade II, 2 Grade II–III, 1 Grade III–IV, 2 Grade IV, 3 primary parenchymal hemorrhage) and 2 are still pregnant (2 IVH II–III). 4 cases were lost to follow up.

#### **Conclusions**

ICH can readily be identified by in-vivo fetal MRI. In contrast to postnatal ICH, grade IV IVH and/or extended parenchymal involvement is not necessarily associated with adverse outcome. Prognostic criteria of fetal ICH will have to be established in the future.

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### P27 Neonatal bilateral occipital brain damage: pattern of damage and outcome

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#### **Aim**

Neonatal bilateral occipital brain damage can cause problems with visual perception and psychomotor development. Outcome data of these patients is limited. The aims of this study are to determine 1) assessment of associated brain damage in infants with bilateral occipital brain injury on MR images and 2) assessment of visual perception and developmental outcome in these patients.

#### **Methods**

We retrospectively studied 19 patients (born 1986–2008) with documented bilateral occipital brain damage on MRI (3 days–18 years). We scored the MRIs for 20 areas of white and gray matter, symmetry, swelling and atrophy. Outcome data were available in 14 patients at three years or above.

#### **Results**

In addition to bilateral occipital brain damage we found abnormalities in the parietal lobe (85%), corpus callosum (77.5%), temporal lobe (40.5%), internal capsule (33.5%), peduncle (23.0%, only seen on DWI), frontal lobe (14.5%) and cerebellum (7.5%). MRI data acquired early (< 34 days) showed swelling and symmetrical abnormalities whereas later MRI findings showed atrophy and less symmetrical damage. Outcome showed visual perception problems in 93% (movement perception 100%, object recognition 62%, color perception 50%). None of the patients were blind. Cerebral palsy (CP) and epilepsy were seen in 83% and impaired cognition in 86%.

#### **Conclusions**

We describe a distinct pattern of brain abnormalities in infants with neonatal bilateral occipital brain damage, mainly associated with neonatal hypoglycemia. Visual perception problems were frequent and included problems with recognition of movement and recognition of objects. Impaired cognition, CP and epilepsy were common.

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### P28 Neonatal diagnosis of a developmental venous anomaly (DVA)

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Developmental venous anomaly (DVA) is the most frequent vascular malformation found in the adult brain. The risk of symptomatic bleeding from DVA is estimated to be 0.2–0.34% per year. It is thought to represent a primary dysplasia of capillaries and small transcerebral veins<sup>1</sup> or a compensatory mechanism caused by intrauterine thrombosis of normal venous pathways<sup>2</sup>. Despite its congenital nature there are no reports of the neonatal diagnosis of isolated DVA. We present four neonates with isolated DVA that were incidentally diagnosed within the first weeks after birth from cranial ultrasound (cUS) and confirmed on magnetic resonance imaging (MRI). In all four the DVA was located in the frontal lobe. In two cases serial cUS in the first postnatal months revealed a remarkable variability in the findings over time with regard to extent and flow velocity. The appearances were generally of a focal fairly uniformly echogenic area adjacent to one frontal horn not typical of injurious processes, which did not break down into cysts or atrophy and which did not encroach on the cortex. We found no evidence for haemorrhage at the time of detection or later. Age of follow-up ranged from 3 months to school age and was normal in all infants.

This is the first case series illustrating that neonatal diagnosis of DVA is possible with carefully performed cUS and MRI. Our knowledge about the incidence, evolution and persistence of DVA in the neonatal period and early infancy is, however, very limited. MRI is increasingly used in neonates; therefore we speculate that this venous anomaly will be more often diagnosed in neonatal brain imaging in the future.

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**P29 Neuronavigated resection of a precentral tumor in a 6-year-old girl: Integration of motor fMRI and MR diffusion tensor tractography**

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### **Aim**

Functional mapping techniques like fMRI and MR diffusion tensor tractography are increasingly integrated in neurosurgical procedures; however, little experience is yet available for children. We report the resection of a precentral tumor in a 6-year-old girl, in whom motor fMRI and MR diffusion tractography proved useful in the preservation of critical motor system components.

Case history: The now 6-year-old girl started with frontal lobe epilepsy at the age of 3 years. She showed painful epigastric auras, atypical absences, and focal clonic and tonic-clonic seizures (left hand/arm) with secondary generalization up to status epilepticus often requiring hospitalization. Seizure control was achieved with OXC and VPA. MRI diagnosed a contrast-enhancing and calcified right precentral tumor immediately anterior to the "hand knob" area, which, after a prolonged period of quiescence, showed rapid growth.

### **Methods**

fMRI: Repetitive squeezing of the examiner's hand<sup>1,2</sup> elicited activation in the "hand knob" area of the right pre- and postcentral gyrus, immediately anterior to the tumor. Tractography identified the cortico-spinal tract, using seed regions in the pre- and postcentral gyrus and in the pons. Data processing was performed using iPlan 2.6 (BrainLab), for both fMRI and tractography. Finally, the identified structures were exported for intra-operative neuronavigation.

### **Results**

After craniotomy, neuronavigation confirmed the anatomically identifiable hand area to harbor the fMRI activation, and to be the origin to the cortico-spinal tract as defined by tractography. Careful resection immediately anterior to the course of the cortico-spinal tract allowed macroscopically complete tumor resection. Post-resectional cortical stimulation showed preserved MEPs. The histology revealed a ganglioglioma. Currently (day 8), the girl recovers from reduced dexterity in her left hand.

### **Conclusions**

Pre-operative motor fMRI is feasible in pre-school children. The integration of these data, together with MR diffusion tractography, is highly valuable for resections in the vicinity of functionally critical structures.

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### P30 Prenatal brain pathology in congenital heart disease

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#### **Aim**

There is growing interest and concern for the neurological morbidity and neurodevelopmental status of infants with congenital heart disease (CHD). Neuroimaging studies performed in children with CHD postnatally (MRI and Ultrasound) revealed cerebral abnormalities. The aim of our study was to identify the type and incidence of fetal brain pathology in fetal heart disease with fetal MRI.

#### **Methods**

A retrospective study was performed. All fetuses were included with a fetal MRI performed after the diagnosis of a heart defect with fetal echocardiography. MR was done on a 1.5T superconducting system. Between 2002 and 2008, 68 fetuses were investigated with fetal MRI. Fetal MRI was performed between GW 20 and 37.

#### **Results**

Cerebral abnormalities were found in 46% (n= 31) . 6/31 fetuses were excluded because of a known chromosomal abnormality and 6/31 had dysmorphic features and unknown karyotyp. 19/31 (28%) fetuses with no additional malformations and normal or unknown karyotyp had a brain abnormality. The most common findings were ventricular asymmetry (incl. ventriculomegaly), agenesis of the corpus callosum and germinolitic cysts.

#### **Conclusions**

Fetal MRI of the brain in CHD is a new method to investigate early onset signs of cerebral changes in fetal brain development. The prenatal origin of brain pathology in such cases was suspected. Fetuses with heart disease had a high percentage (46%) of cerebral abnormalities in the fetal period.

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### P31 Quantitative fiber tracking at term equivalent age in the premature brain: Correlation with MRI findings, GA en PMA

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#### Aim

The aim of this study is to assess the relation between quantitative fiber tracking parameters in the preterm brain at term equivalent age and MRI findings, gestational age (GA) and postmenstrual age respectively.

#### Methods

On a 3.0 T whole-body system, a standard MRI and DTI were acquired in 93 preterm infants with a GA < 31 weeks at term equivalent age. Mean GA was 28.9 weeks (range 25–31 weeks). The DTI sequence used single-shot-EPI with diffusion gradients in 32 directions. To date, 47 patients have been analyzed, of whom ten had to be excluded due to movement artifacts. In-home developed fiber-tracking software was used for analysis of the posterior limb of the internal capsule (PLIC) and the corpus callosum (CC). Regions of interest (ROIs) were drawn manually on the fractional anisotropy (FA)-color-map. Fiber tracking parameters were quantified by calculating the volume of the traced bundle (volume of all pixels through which one or more fibers passed), its length and the average FA and apparent diffusion coefficient (ADC).

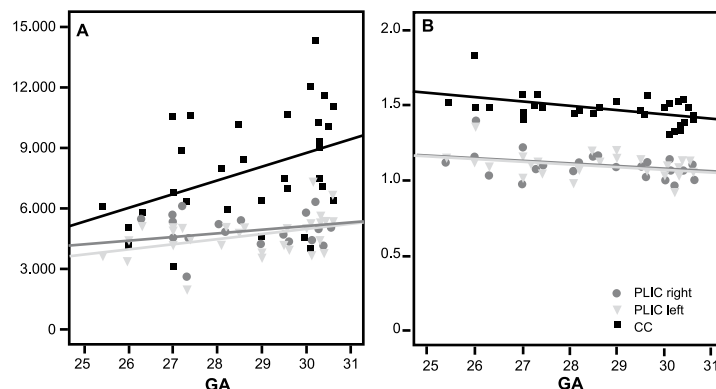
#### Results

A significant difference was observed between the mean FA for left (0.416) and right (0.409) PLIC ( $p=0.008$ ). Fiber bundle volume of CC and left PLIC correlated positively with GA ( $p=0.02$ ), while ADC values correlated negatively with GA, even after correction for postmenstrual age. For the other fiber tracking parameters no correlation could be found (figure 1 below).

#### Conclusions

In the brain of a premature born neonate at term equivalent age fiber volumes of CC and PLIC were larger and ADC values lower in infants with a higher GA. Mean FA values of the right PLIC were higher than of the left PLIC. Neurodevelopmental follow-up is in progress to assess the functional consequences of these findings.

Figure 1: FT parameters (A: volume (mm<sup>3</sup>); B: ADC value)



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**P32 Tractography in 3-month old infants with a perinatal arterial stroke can predict development of hemiplegia.**

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### **Background**

The outcome of perinatal arterial ischemic stroke (PAIS) varies from normal to severe hemiplegia. Previous studies have shown that diffusion tensor imaging (DTI) parameters acquired in childhood differ between hemiplegic and non-hemiplegic children.

### **Aim**

Aim of this study was to investigate whether DTI scans performed at three months in infants with a PAIS can predict development of a hemiplegia.

### **Methods**

Twelve Infants with a PAIS, three of whom had developed hemiplegia as diagnosed at 9-24 months, were included in this study. DTI scans were acquired on a 1.5T Philips MR system at three months postnatal (32 diffusion gradients along non-collinear directions; b-value of 800 s/mm<sup>2</sup>). The datasets were analyzed with the diffusion toolbox ExploreDTI ([www.exploredti.com](http://www.exploredti.com)). Whole brain-tractography was performed with the following thresholds: fractional anisotropy (FA)  $\leq 0.1$ , angle deviation  $\geq 20^\circ$ , and step size 1 mm. Corticospinal fiber pathways intersecting the posterior limb of the internal capsule (PLIC) and the cerebral peduncle were retained. Apparent diffusion coefficients (ADC), FA values, and axial and radial diffusivity were calculated over the entire tract. Symmetry indices were calculated for these parameters, i.e. (value stroke side-contralateral value)/(contralateral value)x100% and were compared with the Mann-Whitney U test between infants with and without hemiplegia.

### **Results**

Symmetry indices were higher for FA (-11.5% vs. -0.1%,  $p < 0.01$ ), ADCs (8.4% vs. -1.5%,  $p < 0.05$ ) and radial diffusivity (33.9% vs. -0.8%,  $p < 0.01$ ) in infants who had developed a hemiplegia. No asymmetry was found in axial diffusivity between both groups.

### **Conclusions**

Asymmetry of the DTI parameters of the corticospinal tract after PAIS can be assessed at three months and can be associated with development of hemiplegia. Though larger studies are necessary, this preliminary analysis suggest that parameters derived from DTI can be used to early predict hemiplegia in infants with a PAIS.

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### P33 Imaging of the basal ganglia and thalami in very preterm infants

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#### **Aim**

To describe imaging findings (cranial ultrasonography (cUS), MRI) of the basal ganglia and thalami (BGT) in very preterm infants, and assess the relation between quantitative measurements, indicative of growth and development, of the BGT and age and white matter (WM) injury.

#### **Patients and Methods**

For 130 very preterm infants (<32 weeks) informed consent was obtained. Sequential, neonatal cUS (all infants) were evaluated for echogenicity of BGT, and term-equivalent MRI (n=110) for changes in myelination and signal in BGT and WM injury. Quantitative measurements (diffusivity values and volumes) of BGT were calculated. BGT changes on cUS and MRI were compared and related to quantitative measurements, age at birth and MRI, and WM injury.

#### **Results**

Bilateral, diffuse, subtle echogenicity of BGT was seen in 92% of very preterm infants. It gradually disappeared with age and was no longer seen after 1 month post-term. No association was found with visual or quantitative BGT changes on MRI. No focal BGT lesions were detected on cUS. One infant had BGT changes on MRI. Quantitative measurements were correlated with age at MRI, but not with gestational age at birth. WM injury was negatively correlated with BGT volumes, but not with diffusivity values.

#### **Conclusions**

In very preterm infants, diffuse, subtle echogenicity of the BGT is a frequent and probably normal prematurity-related finding, while focal BGT lesions are rare. WM injury negatively influences BGT growth.

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### P34 A reversible splenial lesion in patients with delirium associated with influenza

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#### **Aim**

Delirious behavior is one of the main clinical features in patients with clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS). On the other hand, it has been reported that more than 10% of patients with influenza in Japan develop delirious behavior.

Magnetic resonance imaging (MRI) studies in patients with influenza-associated delirious behavior were examined to determine how often a reversible splenial lesion is associated with this symptom.

#### **Methods**

All patients who presented to Kameda Medical Center between November 2007 and March 2008 (07 season), and November 2008 and March 2009 (08 season) with delirium associated with influenza were studied using MRI.

#### **Results**

During the 07 season, 11 of 370 patients with influenza had delirious behavior. All 11 patients had complete clinical recovery. MRI revealed a reversible splenial lesion with homogeneously reduced diffusion in 5 of the 11 patients. All callosal lesions resolved by the time of the follow-up study. On the other hand, during the 08 season, 4 of 520 patients with influenza experienced delirious behavior. No splenial lesion was observed in the 4 patients.

#### **Conclusions**

A reversible splenial lesion with reduced diffusion should be considered as an underlying condition in patients with delirious behavior associated with influenza. The different influenza viruses due to mutations each year might result in a different frequency of a reversible splenial lesion or delirium.

#### **References**

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**P35 Frequency dependent EEG power synchronization correlates with the BOLD signal during working memory**

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Recently, it has been demonstrated that theta EEG power correlated negatively with the BOLD signal in the default mode network (DMN) during rest. In contrast, both alpha global spectral power (GSP) and global field synchronization (GFS) correlated positively with the BOLD signal in the DMN, suggesting GSP and GFS are related.

During working memory (WM) both theta and alpha GSP are negatively correlated with the BOLD signal. However, it is unknown how GFS is linked to GSP and BOLD signal. We parametrically modulated the workload in a visuo-verbal WM task and correlated the GFS and GSP during the retention interval with the BOLD signal in 18 adult subjects.

We demonstrate that theta and alpha GFP BOLD correlations can be replicated in an independent subject sample. Alpha GFS and BOLD were both negatively correlated predominantly in the DMN. Surprisingly, theta GFS correlated positively with the BOLD signal in the DMN with subjects showing weak theta GFS GSP correlations driving this positive relation. Although our findings are preliminary, we suggest that GSP and GFS may show different frequency dependent BOLD correlations.

This study is supported by the University Research Program for Integrative Human Physiology.

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Friday, September 4, 2009, 12:45–14:15

Chair: N. Girard, Marseille, France

**P36 Abnormal glutamate neurotransmission (GNT) in adults with ornithine transcarbamylase deficiency (OTCD)**

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**Objective**

Apply 13C MRS to determine cerebral glutamate turnover rate in OTCD patients and carriers.

**Background**

Neurochemical abnormalities in OTCD resemble hepatic encephalopathy (CHE) in which reduced cerebral glucose metabolism and glutamine–glutamate cycling are believed to impair glutamate neurotransmission (GNT). We hypothesized impaired GNT may underlay the cognitive deficits which commonly develop in treated OTCD.

**Design and methods**

MRI, proton MRS and 13C MRS were performed in 6 OTCD and 4 normal controls who received 13C glucose (0.2 g/kg) C1 or C2, i. v. Cerebral metabolites were determined in posterior (PCG; N=9) and anterior (ACG; N=1) cingulate gyrus over 60 minutes using a clinical GE 1.5 T MR scanner. Results are expressed as rates of change in Glutamate 13C / Glucose 13C.

**Results**

(1) Uptake and removal of cerebral glucose in OTCD was normal ( $P>0.1$ ). (2) Metabolism of glucose C1 to glutamate C4 and of glucose C2 to glutamate C5 were comparable. (3) Glutamate formation rate from either C1 ( $P<0.01$ ) and C2 glucose was reduced in OTCD (combined  $P<0.04$ ). (4) C2 glucose metabolism to glutamate was documented in ACG for the first time.

**Conclusions and relevance**

Treatment of hyperammonemic episodes appears insufficient to preserve cognitive function or normal neurochemistry in adults with OTCD. The cause may lie in reduced GNT secondary to impaired cerebral glucose metabolism. Treatment(s) which improve cerebral glucose metabolism and GNT may improve neurological outcome in OTCD. We demonstrate for the first time that 13C MRS can be safely applied in the human frontal lobe.

Work funded by NIDA (NS), NARSAD (KH); Rudi Schulte Research Institute (BR) and NICHD (AG).

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### P37 Abnormalities of the fornix. A pictorial essay

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#### **Aim**

To bring to the attention of the radiologist to the importance of an accurate analysis of the fornix and to offer a practical approach to the differential diagnosis of abnormalities of the fornix.

#### **Methods**

Using clinical cases and corresponding MRI images, the spectrum of abnormalities of the fornix will be demonstrated. Abnormalities of the fornix can be categorized as abnormalities in size, location and shape.

#### **Results**

Using this approach, the cause of the abnormalities usually fall in the following categories:  
Congenital malformations: Agenesis of corpus callosum, septo-optic dysplasia and the holoprosencephalies and trigono-septal defect  
Acquired lesions: They are often secondary to hydrocephalus, encephaloclastic processes or tumors.

#### **Conclusions**

Accurate analysis of the size, shape and location of the fornix can help the radiologist in the assessment of this often overlooked but vital cerebral structure.

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### P38 Bilateral diffusion tensor abnormalities of temporal lobe and cingulate gyrus white matter in children with temporal lobe epilepsy

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#### Aim

Bilateral diffusion tensor imaging (DTI) abnormalities have been reported in the white matter associated to the hippocampus in adults with mesial temporal lobe epilepsy (TLE). In children with a shorter duration of epilepsy, such changes may not have yet emerged. The aim of this study was to investigate interictal changes in the temporal lobe white matter (TLWM) and cingulate gyrus white matter (CGWM) of children with TLE using DTI.

#### Methods

DTI was performed in eight children with TLE and ten healthy, age-matched controls. Fractional anisotropy (FA), trace, parallel ( $\lambda_{\parallel}$ ) and perpendicular ( $\lambda_{\perp}$ ) diffusivity were calculated for a volume of interest in the TLWM and CGWM on the seizure focus side and the contralateral side. Data was compared for differences between sides for patients and between patients and controls.

#### Results

There was no significant difference in FA, trace,  $\lambda_{\parallel}$  and  $\lambda_{\perp}$  between TLWM and CGWM on the seizure focus side versus the contralateral side in TLE patients. Increased diffusivity,  $\lambda_{\parallel}$  and  $\lambda_{\perp}$  within the TLWM and CGWM were found in TLE patients compared to controls, but no significant difference in FA was seen.

#### Conclusions

Bilaterally increased diffusivity,  $\lambda_{\parallel}$  and  $\lambda_{\perp}$  in the white matter in children with TLE may be related to seizure induced functional or structural changes. The preserved FA in our pediatric cohort is in contrast to the reduced FA in the white matter of adults with TLE and may relate to differences in the duration of epilepsy or in the vulnerability of white matter to seizures.

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### P39 Clinical use of different fiber tracking methods in epilepsy surgery

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#### Aim

For pre-surgical tracking of fibers without a too strong bending usually the FACT algorithm is used<sup>1</sup>. Problems arise, when the fibers are bended strongly like the optic radiation or the fornix, or when a totally abnormal anatomy is present. We evaluated FACT and probability maps<sup>2</sup> for fiber tracking in epilepsy surgery.

#### Methods

Eight children and young adults (mean age 18 years) received a fiber tracking prior to epilepsy surgery. DTI was acquired by a DTI sequence using 61 diffusion directions and a 2x2x2 mm<sup>3</sup> resolution. Patients received an analysis by FACT algorithm and by probability maps. Seed point where derived from fMRI or WFU pick atlas by using spm5.

#### Results

FACT algorithm revealed the corticospinal tract (CST) in an AVM and in a pleomorphic xanthoastrocytoma. It detected the middle longitudinal fascicle in one focal cortical dysplasia (FCD), but failed to detect long association fibers including CST in a case with a hemorrhagic scar. Probability maps were able to show the whole extent of the optic radiation in a cavernoma. In a complex post-therapeutic anatomy of a PNET, probability maps exactly showed the course of the CST. In two cases of abnormal anatomy attributed to cortical dysplasias, the abnormal fiber course could be distinguished by probability maps.

#### Discussion

The FACT algorithm is the mostly used fiber tracking method in presurgical planning. CST and other straight running fibers are delineated by FACT without problems. In the complex anatomy of epilepsy surgery, however, probability maps outperform the FACT algorithm, because an automated pixel-defined start and endpoint are used in this method.

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**P40 Diffusion tensor imaging (DTI) in arginase deficiency shows microstructural damage in pyramidal tract white matter**

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Individuals with a proximal urea cycle disorder (UCDs), such as carbamoyl phosphate synthetase deficiency-1 (CPS-1) or ornithine transcarbamylase deficiency (OTCD), may present with encephalopathy resulting from hyperammonemia. The clinical presentation of arginase deficiency (AD) is significantly different, characterized by progressive spasticity involving the lower extremities and usually dementia. The diagnosis may be delayed and patients are often felt to have cerebral palsy. The true etiology of brain injury in arginase deficiency is unknown, but not believed to be due to hyperammonia and brain swelling, the mechanism of injury recognized in OTCD. Elevated arginine could augment nitric oxide (NO) synthesis, leading to oxidative damage. We hypothesized that a specific brain vulnerability in arginase deficiency would involve microstructural alterations in corticospinal tracts (CST) and that this finding, as measured by diffusion tensor imaging (DTI), would differ from both age matched controls and those with OTCD. We compare DTI data from a 17 year old male with arginase deficiency, age-matched normal controls, and age-matched individuals with OTCD. Significant differences were found in suspected areas of interest, specifically the corticospinal tracts. This finding confirms the hypothesis that the mechanism of injury in arginase deficiency, though unknown, is unlikely similar to that causing OTCD.

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### P41 Diffusion tensor imaging and cognitive profile in partial Ornithine Transcarbamylase Deficiency

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#### Objective

Ornithine Transcarbamylase Deficiency (OTCD) is a genetic disorder of protein metabolism that leads to brain injury. While the early onset form can be globally devastating, partial deficiency leads to specific weaknesses in executive function and motor planning in men, and nonverbal learning disability in women. Less is known about the anatomical basis for this pattern of deficits. Diffusion Tensor Imaging (DTI) allows localization of microstructural abnormalities in the cerebral white matter. Our goal was to identify patterns of white matter injury and cognitive limitations in subjects with partial OTCD.

#### Methods

Our study group consisted of 19 cases and 18 controls who underwent a battery of psychometric tests and brain MRI. MR data for each subject was used to calculate a diffusion tensor then a fractional anisotropy (FA) map. A Region of Interest (ROI) was defined from voxels with statistically different intergroup FA values and was then compared by regression analysis to the results of neurocognitive testing.

#### Results

Analysis of the DTI data revealed an ROI with statistically significant increases in FA confined primarily to the anterior cingulum. Regression analysis showed significant correlations between increased mean FA within the ROI and lower scores in the Stroop and Continuous Trail Making Test.

#### Conclusions

The correlation found between white matter injury, as manifested by increased FA, and deficits in executive function suggest a causal relationship given the known association between the anterior cingulum and executive function. DTI therefore may prove useful clinically to monitor patients with OTCD for early injury.

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**P42 Fetal MRI and fetal autopsy features of embryonal tumor with abundant neuropil and true rosettes**

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**Aim and introduction**

Embryonal tumor with abundant neuropil and true rosettes (ETANTR) is a rare neoplasm which was recently accepted as a distinct sub-entity of CNS primitive neuroectodermal tumors, given its unique histological characteristics overlapping cerebral neuroblastoma and ependymoblastoma, and its female predominance, unlike the other embryonal tumors. To the best of our knowledge, this rare and relatively new entity has never been previously reported in fetal MRI. Our aim is to present the fetal MRI findings in this case and correlate the imaging and the fetal autopsy findings.

**Methods**

A 35 year-old woman with 19 weeks pregnancy was referred to our institution to perform fetal MRI after routine ultrasonography. Fetal MRI was performed on a GE Excite 1.5T system. The pregnancy was interrupted and the fetus underwent autopsy with macroscopical and histological characterization of the tumor.

**Results**

Fetal MRI revealed an infra and supratentorial mass with tentorial, suprasellar and interhemispheric solid component and multiple large cysts associated, exerting mass effect over the adjacent structures, particularly in the posterior fossa. Autopsy revealed a female fetus harboring an intracranial tender, white-colored midline tumoral mass, mainly solid with some cystic areas, arising from the mesencephalic region with both infra and supratentorial extension, measuring approximately 40x30 mm. Histological examination revealed a hypercellular tumor with small cells, abundant neuropils and forming true ependymoblastic rosettes.

**Conclusions**

ETANTR is a rare and recently described subtype of embryonal tumor that, to the best of our knowledge, has never been reported in fetal MRI. Other uncommon features of this case, regarding ETANTR's, are the mesencephalic origin and the presence of large cysts. The authors review the general characteristics of this type of tumor, describe the fetal MRI findings, and illustrate them with macroscopic images from the fetal autopsy.

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### P43 Infant febrile seizures: Do they injure the hippocampus and impair episodic memory?

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Infant febrile seizures (IFS) are often associated with hippocampal sclerosis. As a consequence memory functions that rely on the integrity of hippocampal structures should be impaired. Hence, children with IFS should show selective deficits in hippocampus-dependent episodic memories together with intact context-free semantic memories which are assumed to not rely on the integrity of the hippocampus. In a recognition memory test – an experimental procedure to examine episodic memory – a slow recall-like process by which detailed memories about prior episodes are retrieved (i. e. recollection), should be impaired. In contrast, a second subprocess (i. e. familiarity), by which – similar to semantic memory – context-free memories can easily be recovered, should be unaffected after IFS.

The main goals of the present study were (1) to estimate structural hippocampal damage in IFS children (7–9 years) by means of a MR-based volumetric analysis, (2) to assess semantic and episodic memory abilities using standardized neuropsychological tests, and (3) to assess the relative contribution of familiarity and recollection on the basis of event related potential (ERP) measures.

Our results show that hippocampal volume of IFS children (n=17) was not reduced in our sample relative to age-matched controls. As expected, using neuropsychological tests we found a selective deficit in visual episodic memory and largely spared context-free semantic memories. The ERP-based examination of the subprocesses of recognition memory revealed deficits in recollection, whereas familiarity processing seemed to be unimpaired.

Our data suggest that IFS do not entail a higher risk for hippocampal sclerosis. However, IFS seem to induce functional changes in the MTL memory networks, characterized by a compensation of recollection by context-free familiarity processing.

#### Acknowledgements

This work was supported by Grant KI 1399/1-1 of the German Research Foundation.

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**P44 Microcephaly with simplified gyral pattern: MRI classification**

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**Objectives**

To develop subjective (visual) and objective (morphometric) rating scales for the classification of MRI in microcephalic infants with a simplified gyral pattern (MSGP) and to validate the first by the latter.

**Methods**

We compared the MRI of twelve patients with MSGP and of five term born control infants. Visual rating and morphometric analysis was performed for gyration and associated brain abnormalities of basal ganglia, lateral ventricles, pons, cerebellum and corpus callosum (only visual rating).

**Results**

Gyral pattern was rated reliably as normal in the control infants, simplified in six patients and severely simplified in the other six patients. Associated brain abnormalities were reported in 10 out of 12 patients. Visual rating correlated well with the morphometric measures.

**Conclusions**

Our visual rating scale for a simplified gyral pattern proved to be sensitive and reliable. Associated brain abnormalities are frequent which underlines the need for a consistent scoring in these patients.

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**P45 Movement disorder and neuronal migration disorder due to ARFGEF2 mutation**

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We report a child with a severe choreadystonic movement disorder, bilateral periventricular nodular heterotopia (BPNH) and secondary microcephaly based on compound heterozygosity for two new ARFGEF2 mutations (c.2031\_2038dup and c.3798\_3802del), changing the limited knowledge about the phenotype. The brain MRI shows bilateral hyperintensity of the putamen, BPNH and generalized atrophy. Loss of ARFGEF2 function affects vesicle trafficking, proliferation/apoptosis, and neurotransmitter receptor function. This can explain BPNH and microcephaly. We hypothesize that the movement disorder and the preferential damage to the basal ganglia, specifically to the putamen, may be caused by an increased sensitivity to degeneration, a dynamic dysfunction due to neurotransmitter receptor mislocalization or a combination of both.

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### P46 Neuroradiological findings of 18q deletion (18q-) syndrome

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#### **Aim**

Chromosome 18q deletion syndrome is a rare chromosomal disorder with frequently abnormal intensity of the white matter on T2-weighted images (T2WI) with the following clinical features: developmental delay, growth retardation, hearing loss, hypotonia, craniofacial dysmorphism, foot deformities and eye movement disorders. It is not clear that signal intensity is caused by hypomyelination, though the gene for myelin basic protein (MBP) is encoded on 18q. T1WI and T2WI are frequently reported, however, there is only a few reports of DWI and MR spectroscopy. Our purpose is to discuss the pathogenesis of white matter lesion in 18q-patients on MRI, including DWI and MR spectroscopy.

#### **Methods**

5-year-old boy with 18q-syndrome presents psychomotor retardation, short stature, craniofacial dysmorphism. T1WI, T2WI, DWI (ADC) and MR spectroscopy (PRESS 5000/30, NEX 32, quantitatively analyzed by LCModel) were performed with 1.5 T Siemens apparatus.

#### **Results**

T1WI showed white matter being higher intensity than gray matter, but lower than normal. T2WI showed low intensity in the corpus callosum, but slightly high intensity in the other white matter region with poor gray and white matter contrast. MR spectroscopy revealed normal concentration of NAA, Cr, Cho and Glx, but increased concentration of mIns. The ADC value of the frontal white matter was  $956 \times 10^{-5}$ , showing the medium value of Pelizaeus-Merzbacher disease (PMD) and age matched control.

#### **Conclusions**

The findings of MRS suggested hypomyelination rather than demyelination. ADC value was medium of that of PMD and normal. This suggested that hypomyelination of 18q-syndrome was not so severe as observed in PMD. One of the two normal myelin basic protein gene is normally present in the 18q-syndrome, which may explain why hypomyelination of 18q-syndrome is milder than that of PMD.

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**P47 Does sequential cranial ultrasound predict white matter injury on magnetic resonance imaging in very preterm infants?**

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**Aim**

To prospectively assess the reliability of a classification system for detecting white matter (WM) injury in very preterm infants on frequent, sequential high-quality cranial ultrasound (cUS) throughout the neonatal period, using a MRI classification system as reference standard.

**Methods**

In 110 very preterm infants (<32 weeks), sequential cUS during admission (median 8), and cUS and MRI, using a 3T system, around term equivalent age (TEA) were performed. cUS during admission were assessed for WM changes, and contemporaneous cUS and MRI around TEA additionally for abnormality of lateral ventricles. Sequential cUS up to TEA and MRI were classified as normal/mildly abnormal, moderately abnormal or severely abnormal, based on a combination of findings of the WM and lateral ventricles. Predictive values of the cUS classification for the MRI classification were calculated.

**Results**

cUS were classified as normal/mildly abnormal, moderately abnormal and severely abnormal in respectively 14%, 73% and 13%, and MRI in respectively 25%, 57% and 18% of infants. The positive predictive value of the cUS classification for the MRI classification was high for severely abnormal cUS (0.79) but lower for normal/mildly abnormal (0.50) and moderately abnormal (0.65) cUS.

**Conclusions**

When using the classification system, sequential neonatal cUS up to TEA detects severely abnormal WM in very preterm infants, but is less reliable for detecting mildly and moderately abnormal WM. MRI around TEA is needed to reliably detect WM injury in very preterm infants with normal to moderately abnormal WM.

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**P48 "Rette Calcularis" –a mental number line training for children with developmental dyscalculia**

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Developmental dyscalculia (DD) is a specific learning disability that affects the acquisition of mathematical skills in children with normal intelligence and age-appropriate school education (prevalence 3–6%). According to previous research, children with DD have an impaired representation of the mental number line, also shown by an under-activation of parietal and frontal brain regions. The aim of this study was to develop a specific training program to ameliorate the formation of the mental number line. Twenty children with DD aged 8–10 years completed the computer training "Rette Calcularis" during 5 weeks. The efficiency of "Rette Calcularis" has been evaluated by means of neuropsychological tests and functional magnetic resonance imaging (fMRI) before and after training, as well as, after a rest period of 5 weeks.

Behavioural results indicated a significant improvement in the attribution of numerical magnitudes on a number line, reflecting better spatial representation of numbers. Further we anticipate training-specific alterations in functional brain activity, including the intraparietal sulcus which is thought to constitute the neural correlate of the mental number line.

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