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Summary

Idiopathic epilepsies in childhood normally appear at well distinct, characteristic ages and normally tend to disappear in most of the cases or to respond well to antiepileptic treatment without impairing the development of the child – this is the reason why they can be considered to have a good prognosis. Nevertheless an active epilepsy is able to take influence on congnitive networks, such as language and working memory, dependent on the localisation of focal epileptic discharges. 2 main studies of the UKBB team of pediatric neurology and development are presented which are dedicated to this particular topic.

In the first study, children with constitutional attention deficit disorder have been compared to children with idiopathic epilepsy and attentional deficits. Structural and/or functional differences between these two groups were looked at in detail. Children of both clinical index groups compared to healthy children were found to have similar structural (MRI and fMRI) and functional (neuropsychology) deficits, so that a common pathophysiological basis of these cognitive problems of these groups could be assumed.

The case control study N°2 about children with benign epilepsy with centro-temporal spikes (BECTS) and control children should show the influence of several parameters such as start, duration and degree of severity of epilepsy and the exact localisation of the epileptic focus on language and working memory network and its reorganisation with the help of fMRI, source EEG and neuropsychological testing.

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Key words: epilepsy, attention, language, fMRI, source EEG, neuropsychology

Epilepsie und Kognition im Kindesalter

Idiopathische Epilepsien im Kindesalter weisen aufgrund der Tatsache, dass sie entweder in einem sehr umschriebenen, charakteristischen Alter auftreten und meist auch wieder verschwinden oder aber auf eine antiepileptische Therapie gut ansprechen und die Entwicklung des Kindes nicht massgeblich beeinträchtigen, in der Regel eine gute Prognose auf. Trotzdem kann eine aktive Epilepsie kognitive Netzwerke, so zum Beispiel die der Sprache oder des Arbeitsgedächtnisses in Abhängigkeit ihrer Lokalisation beeinflussen. 2 Hauptstudien aus dem Basler UKBB Team für Neuro- und Entwicklungspädiatrie werden vorgestellt, die sich dem Thema schwerpunktmässig widmen.

In der Studie N° 1 wurden Kinder mit einem konstitutionellen Aufmerksamkeitsdefizit-/Hyperaktivitätssyndrom verglichen mit an einer idiopathischen Epilepsie erkrankten Kindern mit einer Aufmerksamkeitsstörung. Untersucht wurde, ob es strukturelle und/oder funktionelle Unterschiede zwischen diesen Gruppen gibt. Es konnte gezeigt werden, dass die Kinder beider klinischen Indexgruppen verglichen mit gesunden Kontrollen kernspintomographisch und neuropsychologisch vergleichbare strukturelle und funktionelle Defizite zeigen, so dass von einer gemeinsamen pathophysiologischen Grundlage dieser kognitiven Probleme in diesen Gruppen ausgegangen werden kann.

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Die“case control“-Studie N° 2 über Kinder mit einer benignen Epilepsie mit zentro-temporalen Spikes (BECTS) und gesunden Kontroll-Kindern soll den Einfluss diverser Parameter wie Beginn, Dauer und Stärke der Epilepsie, genaue Lokalisation des epileptogenen Fokus mit Hilfe des funktionellen MRIs (fMRI), des Source-EEGs und der neuropsychologischen Testung auf das Netzwerk der Sprache und des Arbeitsgedächtnisses und damit deren Reorganisation aufzeigen.

Schlüsselwörter: Epilepsie, Aufmerksamkeit, Sprache, fMRI, Source EEG, Neuropsychologie

Épilepsie infantile et cognition

Les épilepsies idiopathiques infantiles présentent dans la plupart des cas un pronostic favorable du fait qu'elles surviennent à un âge caractéristique clairement circonscrit, puis disparaissent généralement à nouveau, ou alors elles répondent très bien à un traitement antiépileptique et n'entravent pas sensiblement le développement de l'enfant. Selon sa localisation, une épilepsie active peut néanmoins avoir un impact sur des réseaux cognitifs tels que le langage ou la mémoire de travail. 2 études principales de l'équipe de neuro-pédiatrie et pédiatrie développementale du Centre pédiatrique universitaire des deux Bâle (UKBB) sont présentées qui ont fait de ce thème leur priorité.

Dans l'étude numéro 1, des enfants avec un syndrome constitutionnel de déficit de l'attention/hyperactivité ont été comparés avec des enfants atteints d'une épilepsie idiopathique accompagnée d'un trouble déficitaire de l'attention. L'étude s'intéressait à la question de savoir s'il existait des différences structurelles et/ou fonctionnelles entre ces deux groupes. L'examen par tomographie à spin nucléaire et neuropsychologique a permis de montrer que les enfants des deux groupes d'indices présentaient des déficits structurels et fonctionnels similaires en comparaison avec des témoins sains, ce qui étaye l'hypothèse d'une base pathophysiologique commune des problèmes cognitifs dans ces deux groupes.

L'étude numéro 2 de cas témoins d'enfants avec une épilepsie bénigne à pointes centro-temporales (BECTS) et de sujets témoins sains doit montrer à l'aide de l'IRM fonctionnel (IRMf) et du testage neuropsychologique le retentissement de divers paramètres tels que le début, la durée et l'intensité, ainsi que la localisation exacte du foyer épileptogène, sur le réseau du langage et de la mémoire du travail.

Mots clés : épilepsie, attention, langage, IRMf, source EEG, neuropsychologie

Introduction

In most cases, idiopathic epilepsy in childhood has a good prognosis, either because in age-related epilepsies seizures occur only in a narrow time window of development and brain maturation, and/or because a seizure-free situation can be achieved by an antiepileptic treatment.

However, the long-term prognosis in childhood epilepsy is not only determined by the frequency and intensity of seizures, but also by associated condition in social, emotional and cognitive development. Therefore it has to be recommended, that clinical counselling as well as the scientific efforts include these important topics for successful socialisation in children with an epileptic disorder.

In the scientific work the Division of Neuropediatrics and Developmental Medicine, University Children Hospital Basel focuses neuropsychological aspects of childhood epilepsy. In this context this manuscript reports about two projects in which attention problems and cortical reorganisation of language in children with epilepsy are mentioned.

Study project N°1: Attention deficit/hyperactivity disorder in childhood epilepsy

Based on earlier own studies about cognitive profile [1] and attention-induced cortical hemodynamic responses in children with attention deficit hyperactivity disorder (ADHD) [2, 3] the functional and structural cortical and cerebellar conditions in children with epilepsy and ADHD were investigated.

Study 1a:

Decreased fractional anisotropy in the middle cerebellar peduncle in children with epilepsy and/or ADHD

Author: Bechtel N [4]

Study 1b:

Neuropsychological and attention induced cerebral hemodynamic effects in children with epilepsy and attention deficit/hyperactivity disorder

Author: Bechtel N [5]

Background

Attention problems are one of the most frequently associated cognitive problems in children with epilepsy. Compared with a prevalence of attention deficit disorder in school-age children of 5% [6] the latter is reported in up to one of three children suffering from epilepsy [7, 8]. The reason for this increased risk is unknown. Interestingly, attention problems are not only observed in children, who suffered from intractable or long standing seizures or who were treated by anticonvulsive drugs, which could decrease attention as an adverse effect, but it is also observed with a higher frequency before the first seizure occurs. Therefore we investigated through neuropsychological and functional MRI procedures, if the attention problems from children with epilepsy and ADHD are different from attention problems in children with pure ADHD.

In a first study [4] we focused on cerebellar structure and its features in attention problems. Some studies underline cerebellar abnormalities on a structural level in children with ADHD. Smaller cerebellar hemisphere volumes as well as decreased cerebellar vermis volume were described [9, 10]. In a further study using diffusion tensor imaging, a new magnetic resonance sequence, a significant decrease of fiber organization in children with ADHD was measured in right cerebral peduncle, left middle cerebellar peduncle as well as in left cerebellum [11].

Therefore we investigated structural features in children with developmental ADHD and ADHD associated with epilepsy. The aim of this study was to clarify whether attention deficit in both groups is associated with different or same structural abnormalities focussing on cerebellum.

We investigated eight boys with combined epilepsy/ADHD (mean age 11.6 years (SD 1.69), 14 boys with developmental ADHD without any other neurological disease (mean age 10.4 years (SD 1.34), and 12 healthy controls (mean age 10.9 years (SD 1.62)). All three groups showed a comparable intelligence. The symptom severity measured by the short version of Conners' Scale for Parents [12] was comparable between the two index groups. The boys of the epilepsy group suffered from idiopathic focal epilepsy.

The imaging procedure was performed on a 3-T MRI scanner using voxel-based diffusion tensor imaging generating fractional anisotropy. The results demonstrated that healthy controls exhibited more fractional anisotropy, a marker for structural organization, than the boys of both clinical groups in the left as well as in the right middle cerebellar peduncle and in the right hemisphere of the cerebellum. No differences were documented between both clinical groups.

In summary, this study data yield information that an attention deficit disorder as a developmental disorder as well as in association to epilepsy is linked to the same structural abnormalities in the cerebellum, especially to the connection between cerebellum and pons as part of the cortico-ponto-cerebellar network, which is largely involved in several executive functions [13]. The cerebellum seems not to be largely involved in epileptic activities. Therefore it could be assumed, that first cerebellar differences are not mainly caused by epilepsy and second attention deficit disorder could have the same neurobiological background in children with or without epilepsy.

In a second study [5] we investigated possible differences in working memory between healthy controls and boys with pure ADHD and ADHD associated with idiopathic focal epilepsy. Working memory is one of the most frequently and robustly reported executive function deficit in children with ADHD. Several functional neuroimaging studies reported decreased neuronal activation in the cortical network involved in working memory achievement [14]. Again the aim of this study was to answer the question whether working memory capability is different in children with ADHD compared to healthy controls and whether differences exist between children with pure ADHD and ADHD associated with epilepsy in respect to working memory capabilities.

To investigate this question we examined behavioural differences in working memory performance and functional brain organization in children with epilepsy/ADHD, children with pure ADHD and healthy controls.

17 boys with epilepsy and ADHD, 15 boys with pure ADHD and 15 healthy boys were included in the study group. Age ranged from eight to 14 years, only boys were recruited to create a higher homogeneity of the study groups.

Again, the groups did not differ in intelligence.

Working memory performance was examined through n-back tasks (0-back, 2-back, and 3-back tasks.). To measure the behavioural data, reaction time and reaction accuracy of the answer were measured. To investigate the cortical activation fMRI measurements were done, using a 3T-MRI scanner, during scanning N-back tasks were presented.

Behavioural healthy controls performed with a significantly better accuracy compared to boys with ADHD and epilepsy in the 2-back task and in tendency in the 3-back task. Comparing healthy controls and patients with pure ADHD the first one achieved significantly better results in both tasks.

On the functional level both patient groups (pure ADHD as well as epilepsy-associated ADHD) showed similar reductions of activation in all relevant parts of the functional network of working memory if compared to healthy controls. The differences included parts of frontal lobes as well as parts of the parietal lobes and involved structures of the cerebellum.

Conclusion

Both studies showed a structurally and functionally high similarity of brain features and cerebral hemodynamic responses in both groups of boys with ADHD – pure ADHD and epilepsy-associated ADHD. Although the prevalence of ADHD is nearly six-fold higher in children with epilepsy, the neurobiological pathophysiology seems to be similar. Therefore our data support the idea that ADHD with or without epilepsy shows a common aberrant network of working memory and hypothesizedly of attention deficit. In view of these results it seems to be adequate, that the same therapeutic procedures are indicated, psychopharmacological as well as behavioural treatments.

Study project N° 2: Language and cortical reorganization in childhood epilepsy

Language and motor fMRI, EEG-Source Imaging and neuropsychology: a case control study about language and fine motor impairment and cortical reorganisation in children with benign epilepsy with centro-temporal spikes (BECTS).

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Collaborators: Lantz G, Michel CM (Geneva), Hertz-Pannier L (Paris), Maier O (St. Gallen), Ramelli GP (Bellinzona), Martin F (Aarau), Bauder F (Luzern)
This study is still in process.

Background

BECTS occurs in 8 - 23% of children with epilepsy [15]. Epileptic discharges are clearly amplified during sleep and most seizures are occurring in the night mostly in early morning. The age of seizure onset is between 3 and 14 years with a peak of frequency between 5 and 8 years. In idiopathic epilepsies, the child's intelligence is normal and no other neurological deficits should be present due to epilepsy [16, 17]. Nevertheless, idiopathic epilepsy can affect neurological integrity of these children causing deficits [18] and although epilepsy is considered to be a paroxystic disorder causing epileptic seizures, a durable alteration of certain cortical functions such as regression, stagnation or temporary loss of certain cognitive functions can also be a direct manifestation of epilepsy [19].

Neuropsychological deficits in children with BECTS have been reported. Beside deficits in non-verbal functions especially language related dysfunctions were documented such as delayed reading, numerancy and spelling [20], delayed language development with mixed phonological and lexico-syntactic problems [21], deficits in verbal fluency, verbal reelaboration, semantic knowledge and lexical comprehension [22, 23]. Language lateralization evaluated with neuropsychological testing in children with BECTS has been shown to be atypical [24]. Adolescents and young adults in remission from BECTS even show slightly lower performance IQs and different organizational patterns for language [25].

Some studies support the hypothesis that paroxysmal abnormalities and cognitive functioning are linked and that interictal discharges could lead to transient cognitive impairment depending on the localisation of the focus [26, 27]. Other authors hypothesize that developmental transitory dysfunctions of cell migration and differentiation in the granular layer might lead to circumscribed cognitive deficits and to the appearance of focal discharges; once the cerebral development is completed, the deficits and the discharges are supposed to disappear. But even so, repeated ictal and interictal discharges might lead to persisting deficits.

The pathways of language have already been widely studied with fMRI in healthy adults or patients [28, 29] but there is relatively little data in children mainly because of methodological differences specific to this population: several studies have started to approach the study of language networks in healthy children (30-33) providing reference data for the study of pediatric patients. It is already known that language functions are preferentially lateralized to the dominant hemisphere in early childhood and that the preferential modality of reorganization in the case of a lesion to this hemisphere is by relocation to the non-dominant hemisphere in a mirror-image of normal organization [30]. The implication of the central region in the epileptic disorder seems to play a crucial role in contralateral language reorganization.

Until now, only few studies have been investigated the plasticity of language in the epileptic children (34 - 37) and to our knowledge only one study was done in children with BECTS where language was found to be less lateralized to the left hemisphere in anterior language ROIs [38]. Language disorders is a good documented developmental delay in children with BECTS, formerly investigated in Switzerland by T. Deonna, E. Roulet and co-workers. To investigate this problem and processes of language reorganization will progress our understanding of processes of language development as well as the influence of epileptic discharges and seizures on the development of language. To get a comprehensive understanding of these processes a combination of neuropsychological and neurophysiological methods as well as functional neuroimaging is requested.

Material

20 patients with a diagnosis of BECTS have been recruited in the Divison of Neuropediatrics and Developmental Medicine in the University Childrens' Hospital Basel (UKBB); recruitment will be soon completed. Patients from neuropediatric centers like St. Gallen, Aarau, Bellinzona and Luzern have also participated in the study.

BECTS-patients with deficits in expressive or receptive speech (detected by history and confirmed by neuropsychological testing) or fine motoricity (confirmed by neurological examination) are compared to BECTS-patients without such deficits concerning their language laterality index (language and motor fMRI) and their spike or sharp wave localization (Source EEG).

20 healthy gender-matched children without epilepsy corresponding with a similar age group of each patient (+/- three months).

The aims of the study

The aim of this case control study is to find out if BECTS not only causes deficits in language performances confirmed by neuropsychological tests and fine motor impairment by neurological examination, but that these deficits are as well correlated with a functional reorganization of the language and fine motor networks. A good indicator to evidence the reorganisation capability in children with BECTS is the laterality index (LI). The impact of the exact localization of the epileptic focus, the onset and severity of epilepsy on reorganization of language and fine motor networks are investigated. For this, children with BECTS are compared to healthy children.

The questions of the study are:

- Is the laterality index (LI) of language and fine motor behaviour of patients with BECTS significantly lower than LI of healthy children in respect to their age?
- Does a correlation exist between the LI of patients with BECTS and

a. the age of onset of epilepsy,
b. the duration of epilepsy, defined by the time between onset of epilepsy and time of investigation
c. the severity of epilepsy, defined by the frequency of seizures
d. the exact location of the epileptic focus in the Rolandic area,
e. the duration and actual existence of an antiepileptic drug treatment and
f. neuropsychological and motor deficits?

Methods

To answer the study questions, several examinations are done including the following procedures:

a. fMRI with language and motor tasks
b. EEG Source Imaging recording
c. Neuropsychological examination
d. Neurological examination

a. functional MRI

FMRI as a method offering high sensitivity to local changes in cerebral blood oxygenation are used to detect differences in brain activation between children with epilepsy and healthy controls during different tasks.

Three language tasks, three working memory tasks and one motor task are used for this study. Acquisitions in blocks are made on a 3T MR-scanner (Siemens Verio) as described in previous studies [35, 39, 40]. The three language tasks are silent generation of simple sentences (subject-verb-complement) (task n°I), silent generation of words by category (task n°II) and reading (task n°III). All tasks consist of five blocks of resting and four activation blocks. One activation block contains five stimuli, each presented for five seconds. In resting blocks the projected stimuli are replaced by a fixation cross.

b. EEG (3D-EEG source imaging)

For 3D-EEG source imaging patients undergo a 64-channel scalp surface recording on an EGI-EEG-system. 64 electrodes are placed as a “hat” on the head of the patient. 64 electrodes are crucial for sourcing deep foci in the insular or in the lower temporal region.

For Source Imaging, 20 artefact-free interictal spikes or sharp waves with similar surface voltage distribution are selected from the recording with 64 electrodes. Spikes get aligned and further analyses determine the brain areas of significant electric signal increase during the sharp wave or the spike. Then statistical parametric mapping (SPM) approach to compute voxel-wise t-tests between two conditions is used [41, 42]. Finally, the results are reconstructed on 3 Tesla MR-images.

Localization of intracerebral generators from the scalp EEG, developed during the last few years, have been effectively applied to epileptic data [42-44]. In a recent study of epileptic children during presurgical workup, 3D analysis of interictal epileptic activity using standard EEG recordings provided good results in terms of epileptic focus localization [41]. The localization precision is especially high, when EEG is recorded with a larger number of electrodes (64 electrodes), especially concerning low and mesio-temporal foci [42, 45].

c. Neuropsychology

A complete neuropsychological examination procedure is administered to each child by a neuropsychologist with the Hamburg-Wechsler-Intelligenztest for Children (HAWIK-IV) [46], including an age-adequate verbal and non-verbal intelligence scale. This test battery assesses various aspects of oral language including denomination, comprehension and verbal fluency, logical reasoning and processing speed, verbal memory and verbal working memory. Further more the visual spatial memory and the visual spatial working memory (Corsiblock forward, Corsiblock backwards), visual working memory (N-back test, one, two, three), as well as a test of handedness (Hand-Dominanz-Test, HDT) [46-48].

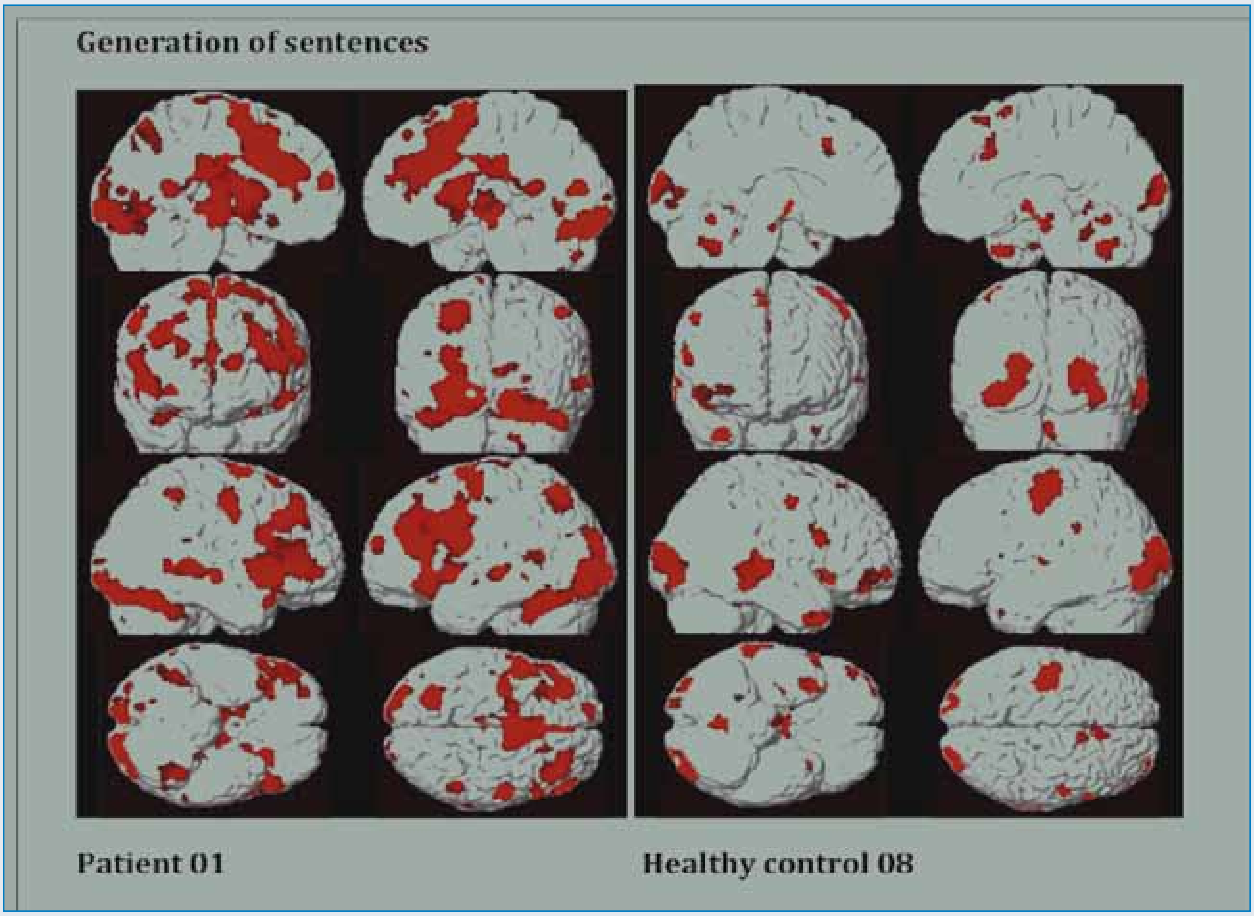


Figure 1: fMRI: Patient 01 shows a more bilateral activation of the language network in the task „generation of sentences“ in contrast to the control 08.

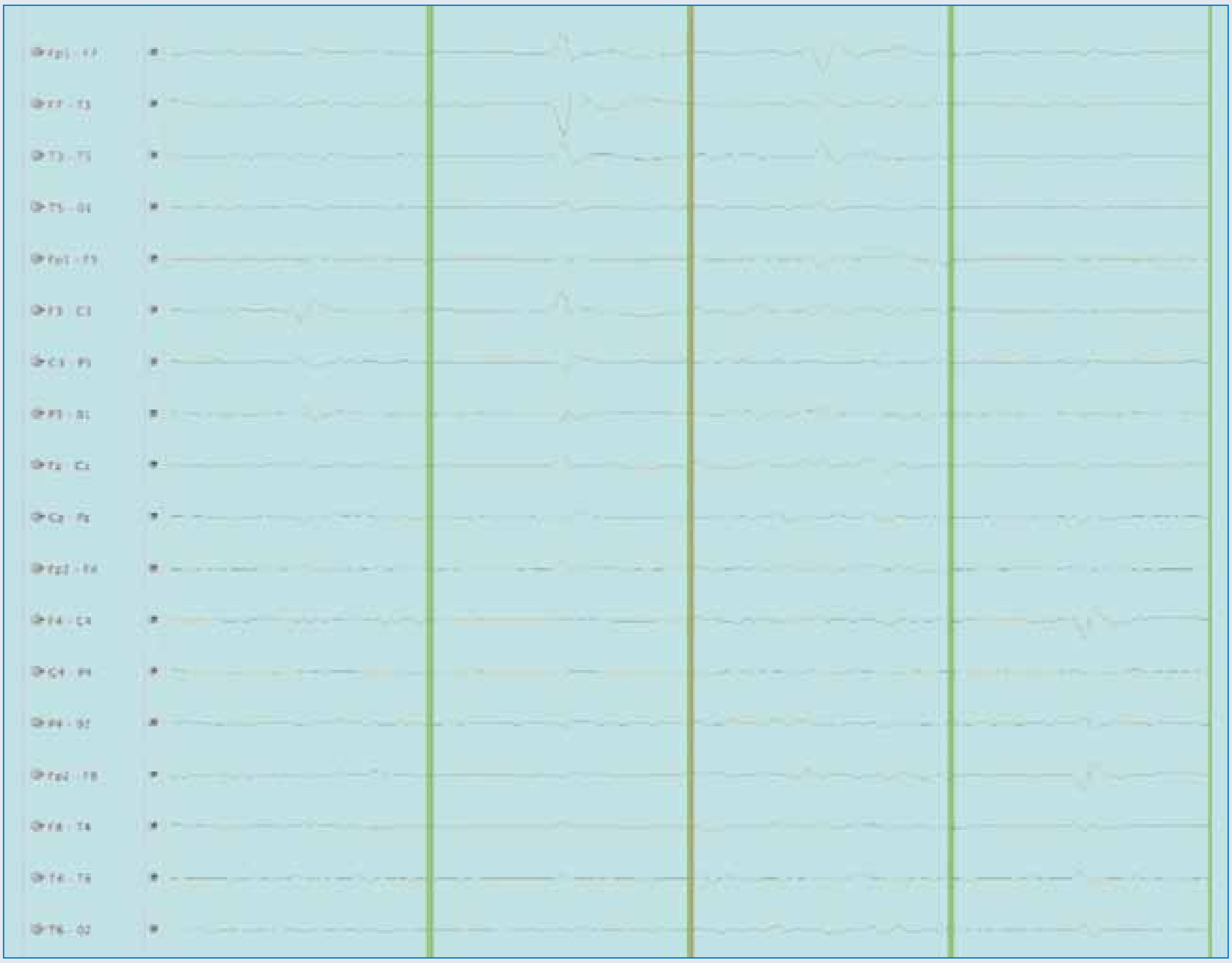
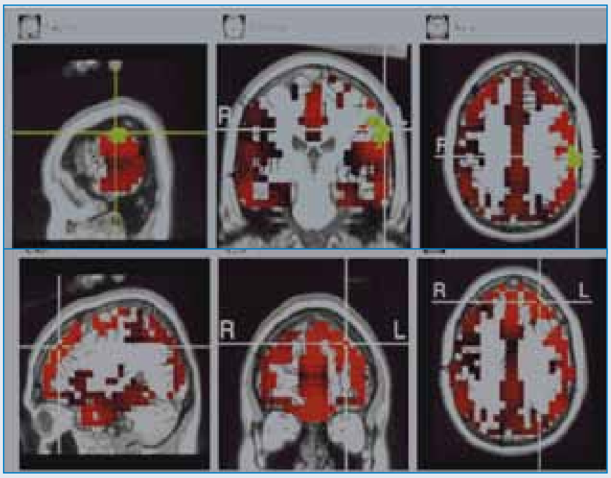


Figure 2: EGI EEG system: Localisation of 4 sharp wave foci in one patient: Three on the left and one on the right hemisphere.



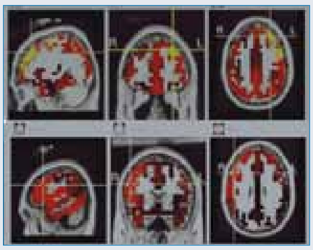


Figure 3: Source localisation results projected on a template: 4 different sharp wave foci in one single patient (corresponding to sharp waves in figure 2)

Data analysis

The analysis of statistical parametric mapping in EEG Source Imaging was performed using the GeoSource software. GeoSource is a set of tools to model the neural sources of the brain's electrical fields (EGI; Electrical Geodesic, Inc., 2008; www.egi.com). Post-processing and statistical analysis of fMR images are performed using SPM5 (Statistical Parametric Mapping, Welcome Department of Cognitive Neurology, University College London). Numerical procedures and calculations to assess these parameters get implemented in MatLab.

The clinical parameters are correlated with the results of fMRI, focus results of EEG Source Imaging as well as with the results of neuropsychological examinations with simple t-Test correlations, multiple regression analysis and multivariant analysis between subjects and between groups.

Outlook

Childhood epilepsies can interfere with the development of cognitive functions because the pathways of epilepsy are often the same as the cognitive pathways. Because of this, epilepsy is an important model for studying not only reorganisation capacities in pathological conditions, but also for a better understanding of normal development of the brain and the mechanisms of learning. Functional development of the brain is maximal during early childhood. The earlier the onset of epilepsy, the deeper the impact on cognitive function usually is. Also the reorganisation capacities of the pathways are maximal in the young child. However different functions (i.e. motor, visual, language, memory) develop at different ages and it is during the period of maximal development that the pathways are the most likely to be altered by a pathological phenomenon and that they have the best capacities for reorganisation. Functional MR studies are therefore important to make functional reorganisation visible. A better representation of dynamics of reorganisation can be achieved by longitudinal studies; together with studies N° 1 and 2, but in particular with our longitudinal follow-up project in newly diagnosed BECT patients (we will shortly start with) we will hopefully give interesting answers to this topic.

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