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### Allgemeines

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### Was ist an die Redaktion einzureichen?

Alle Manuskripte sind inklusive Abbildungen und Tabellen in dreifacher Ausführung einzureichen. Bevorzugt wird eine elektronische Manuskripteinreichung per e-mail (Textverarbeitung: MS Word), alternativ die Zusendung von drei Ausdrucken und einer Diskette (für Abb. und Tab. ist das verwendete Programm anzugeben).

PD Dr. med. Dr. sc. nat. Kaspar Schindler



Die Hauptfunktion des zentralen Nervensystemes ist die rasche Informationsverarbeitung, welche ihr physikalisches Substrat in bioelektrischen Prozessen findet. Vereinfachend auf den Punkt gebracht: das Hirn ist im Wesentlichen ein elektrisches Organ. Dies ist einer der Hauptgründe, weshalb die Elektroenzephalographie, hier weit gefasst definiert als die Aufzeichnung elektrischer Signale des zentralen Nervensystemes, auch fast hundert Jahre nach ihrer ersten Anwendung am Menschen durch Hans Berger eine unverzichtbare technische Zusatzuntersuchung der modernen Epileptologie bleibt. Ein weiterer wichtiger Grund für die Aktualität der Elektroenzephalographie ist auch, dass sie ständig weiter entwickelt wird. Darüber soll in diesem Heft berichtet werden.

In dem ersten Artikel beschreibt Julia Jacobs die in den letzten Jahren entdeckten Hochfrequenzoszillationen (HFO) im Bereich von 80-500 Hz, wie sie technisch erst registriert werden konnten, nachdem digitale EEG-Verstärker mit hohen Abstraten zum Einsatz kamen. Die Autorin diskutiert die methodischen Voraussetzungen zur sicheren Aufzeichnung und Analyse von HFO und sie zeigt, dass diese raschen EEG-Signaloszillationen potenziell sehr gute Biomarker für epileptogenes Gewebe sind. Die daraus folgenden Implikationen für Diagnostik und Therapie bei pharmakoresistenten Epilepsien sind ausgesprochen wichtig.

Augustina Maria Lascano et al. geben in ihrem Artikel eine umfassende Übersicht über die neuen Möglichkeiten, die intrakraniell gelegenen elektrischen "Quellen" von mit Hautoberflächen-Elektroden nicht invasiv gemessenen EEG-Signalen zu rekonstruieren. Theoretische Grundlagen, praktische Durchführung und Resultate klinischer Studien mit diesem wichtigen Verfahren werden sehr anschaulich und anhand von Patientenbeispielen eindrücklich demonstriert.

Martinus Hauf et al. beschreiben, wie nicht invasives EEG mit gleichzeitigen fMRI-Messungen kombiniert werden kann, um die hohe zeitliche Auflösung des EEG mit der hohen räumlichen Auflösung des fMRI vorteil-

haft zu nutzen und auf diese Art die Hirnareale zu identifizieren, welche für die Entstehung der an der Hautoberfläche gemessenen epilepsietypischen elektrischen Signale verantwortlich sind. Möglichkeiten und Grenzen dieser technisch anspruchsvollen Methode werden diskutiert.

Die modernen technischen Entwicklungen wie zum Beispiel die Möglichkeit, EEG-Signale mit hoher Abtastrate aufzuzeichnen, führen zu immer grösseren Datenmengen. Um die darin enthaltene diagnostisch und therapeutisch relevante Information zu erkennen, werden quantitative Analysemethoden immer wichtiger. Christian Rummel et al. erörtern deshalb in einem Überblick verschiedene Methoden der quantitativen Analyse periiktaler EEG-Signale. Dabei werden die Methoden systematisch nach uni-, bi- oder multivariatem Charakter eingeteilt und beschrieben, und es wird auch auf die Möglichkeit eingegangen, gerichtete Interaktionen zwischen EEG-Signalen zu erfassen.

Schliesslich beschreiben Claudio Pollo et al. die neuesten faszinierenden technischen Entwicklungen auf dem Gebiet der Multi-Elektroden-Arrays, wie sie ausgiebig im Tierversuch getestet, aber auch zunehmend bei Menschen eingesetzt werden. Diese neuen Elektroden ermöglichen eine bisher nie dagewesene raumzeitliche Auflösung der hirnelektrischen Aktivität in vivo. Sie liefern dadurch wichtige Einsichten in die Dynamik der Anfallsentstehung und -ausbreitung, und sie werden mit hoher Wahrscheinlichkeit in Zukunft dazu beitragen, die Diagnostik und Therapie der Epilepsien wesentlich zu verbessern.

Wir hoffen, die hier publizierten Artikel überzeugen Sie, dass die Elektroenzephalographie auch nach fast hundert Jahren klinischer Anwendung nichts von ihrer Faszination und Relevanz verloren hat – im Gegenteil.



Kaspar Schindler



*PD Dr. med. Dr. sc. nat. Kaspar Schindler*

The main purpose of the central nervous system is to rapidly process information. Information however is physical, and the only physical substrate suitable to implement rapid information processing is bioelectricity. In a nutshell, the brain is basically an electrical organ. This is one of the main reasons why electroencephalography, here broadly defined as the recording of electrical signals generated by the central nervous system, remains an indispensable method of modern epileptology, even almost one hundred years after its first application to humans by Hans Berger. Another important reason for the timeliness of electroencephalography is its constant development, which is the theme of the present issue.

In the first article Julia Jacobs describes high frequency oscillations (HFO) in the range of 80-500Hz, which have only recently been discovered after the introduction of digital amplifiers with very high sampling rates. The author discusses methodological prerequisites to reliably record and analyse HFO and she clearly demonstrates that these high frequency signals are potentially excellent biomarkers for epileptogenic cortex. The implications of these findings for diagnosis and therapy of pharmaco-resistant epilepsy are of highest importance.

Augustina Maria Lascano et al. give a comprehensive and fascinating overview about the latest methods of electrical source imaging, i.e. techniques to non-invasively delineate the brain regions that generate EEG signals as recorded by scalp electrodes. Theoretical basics, practical procedures and results of clinical studies are demonstrated using very illustrative and impressive cases.

Martinus Hauf et al. describe how non-invasive EEG may be combined with simultaneous fMRI studies to make use of both the high temporal resolution of EEG and the high spatial resolution of fMRI. The goal of combining these techniques is to detect the brain regions that generate surface EEG signals. Possibilities

and limits of this technically demanding approach are discussed.

Modern technological developments like the possibility to record EEG signals with high sampling rates yield an ever increasing amount of data. In order to detect the diagnostically and therapeutically relevant patterns contained in this flood of information it becomes mandatory to invoke quantitative and computer based methods. Therefore Christian Rummel et al. discuss several quantitative methods used for analysing periictal EEG signals. They follow a systematic approach and categorize methods according to being uni-, bi- or multivariate and they also describe the important possibility to detect directed interdependences between signals.

Finally, Claudio Pollo et al. describe the latest technical developments in the fascinating field of so-called multi-electrode-arrays, which have already been extensively tested in animal experiments and are now increasingly often applied to record human EEG, too. This new kind of electrodes makes it possible to record neuronal activity in vivo with unprecedented spatiotemporal resolution. The signals recorded by these electrodes provide important insights into the dynamics of seizure generation and propagation and it is to be expected that they will help to significantly improve diagnostic and therapeutic procedures in pharmaco-resistant epilepsy in the very near future.

We hope that these articles are convincing evidence for the continuing fascination of electroencephalography and its unbroken relevance for clinical epileptology.

A handwritten signature in blue ink that reads "Kaspar Schindler".

*Kaspar Schindler*

*PD Dr. med. Dr. sc. nat. Kaspar Schindler*



La fonction majeure du système nerveux central est le traitement rapide de l'information qui trouve son substrat physique dans des processus bioélectriques. Ou pour simplifier: le cerveau est essentiellement un organe électrique. C'est une des principales raisons pour lesquelles l'électroencéphalographie, définie ici dans un sens large en tant qu'enregistrement des signaux électriques du système nerveux central, reste un examen technique complémentaire indispensable de l'épileptologie moderne près de cent ans après sa première utilisation sur l'être humain par Hans Berger. Une autre raison qui fait que l'électroencéphalographie reste d'actualité, c'est qu'elle ne cesse d'être perfectionnée. Et c'est de ces développements que parle le présent numéro de notre revue.

Dans le premier article, Julia Jacobs décrit les oscillations haute fréquence (HFO) découvertes ces dernières années dans une plage de 80-500 Hz avec l'aide des nouvelles technologies et le développement d'amplificateurs numériques à taux élevé de balayage. L'auteure discute des conditions méthodologiques requises pour garantir un enregistrement et une analyse fiables des HFO et elle montre que les oscillations rapides des signaux de l'EEG ont le potentiel d'être d'excellents biomarqueurs de tissus épileptogènes : il en découle des implications de la plus haute importance pour le diagnostic et le traitement des épilepsies pharmaco-résistantes.

Dans leur article, Augustina Maria Lascano et al. font un tour d'horizon très complet des nouvelles possibilités de reconstruction des « sources » électriques dans la zone intracrânienne de signaux de l'EEG mesurés par des méthodes non-invasives au moyen d'électrodes appliquées à la surface de la peau. Les bases théoriques, l'exécution pratique et les résultats remarquables d'études cliniques réalisées avec ce procédé sont expliqués de manière très claire et illustrés par les cas concrets de patients.

Martinus Hauf et al. décrivent comment on peut

combiner simultanément un EEG non-invasif et des mesures fMRI pour profiter à la fois de la haute résolution temporelle de l'EEG et de la haute résolution spatiale du fMRI en vue d'identifier les zones du cerveau qui sont responsables de la genèse des signaux électriques épilepsie-typiques mesurés à la surface de la peau. Les possibilités et les limites de cette méthode d'une technicité exigeante sont discutées dans l'article.

Les technologies modernes telles que l'enregistrement des signaux de l'EEG avec un taux de balayage élevé nous fournissent des données de plus en plus volumineuses. Dans cette pléthore d'informations, il s'agit de repérer celles qui ont une importance pour le diagnostic et le traitement et à cet effet, on fait de plus en plus appel aux méthodes de l'analyse quantitative. Christian Rummel et al. discutent les différentes méthodes d'analyse quantitative des signaux péri-ictaux de l'EEG. Les méthodes sont systématiquement classées et décrites en fonction de leur caractère uni-, bi- ou multivarié et l'article s'interroge sur la possibilité de capter des interactions orientées entre signaux de l'EEG.

Enfin, Claudio Pollo et al. évoquent les récents développements techniques particulièrement captivants du domaine des multi-électrodes extracellulaires (MEA) qui ont été abondamment testées dans l'expérimentation animale et sont aussi de plus en plus utilisées chez l'être humain. Ces nouvelles électrodes permettent une résolution spatio-temporelle jusqu'ici inégalée de l'activité électrique du cerveau in vivo. Elles fournissent de ce fait des enseignements importants sur la dynamique de la genèse et de la propagation des crises et contribueront très probablement dans le futur à améliorer considérablement le diagnostic et le traitement de l'épilepsie.

Nous espérons que les articles publiés dans ce numéro parviendront à vous convaincre qu'après presque cent ans d'application clinique, l'électroencéphalographie n'a rien perdu de sa fascination et de son importance – bien au contraire.

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### Zusammenfassung

Patienten mit therapierefraktärer Epilepsie profitieren von sicheren Biomarkern für epileptogene Areale. Im intrakraniellen EEG konnten nun neben interiktalen Spikes und der Analyse des Anfallsursprungs Hochfrequenzoszillationen (HFO) als potenzielle Marker für epileptogene Areale identifiziert werden. Diese HFO liegen im Frequenzbereich zwischen 80 und 500Hz, sind nur wenige Millisekunden kurz und werden über sehr kleinen Hirnarealen generiert. Im Tiermodell konnte ein enger Zusammenhang zwischen epileptischen HFOs und Epileptogenese gefunden werden. Auch bei Patienten mit therapierefraktärer Epilepsie können HFOs genutzt werden, um epileptogene Areale zu identifizieren. Die operative Entfernung von Arealen, über denen HFOs generiert werden, korreliert mit der postoperativen Anfallsfreiheit. Erste Studien zeigen, dass HFOs nicht nur im intrakraniellen EEG, sondern auch im Oberflächen-EEG einen interessanten EEG-Marker darstellen könnten. Dieser Review diskutiert, welche methodischen Voraussetzungen erfüllt werden müssen, um HFOs sicher aufzuzeichnen und zu analysieren. Weiterhin werden die verschiedenen klinischen Einsatzmöglichkeiten von HFOs dargestellt und offene Fragestellungen aufgezeigt, die vor dem weiten klinischen Einsatz von HFOs geklärt werden müssen.

**Epileptologie 2012; 29: 70 – 79**

**Schlüsselwörter:** Ripple, Fast ripple, Hochfrequenzoszillationen, Epilepsiechirurgie, Spikes

### High Frequency Oscillations (80-550Hz): A Clinical Marker for Epilepsy?

In patients with refractory epilepsy there is a need for reliable markers of epileptogenic areas. Interictal epileptic spikes and the seizure onset zone are the most used clinical markers in intracranial EEG. High frequency oscillations (HFO) between 80 and 500Hz might be novel EEG markers. In animal models a clear correlation between the occurrence of HFOs and the development of chronic epilepsy could be found. In patients with refractory epilepsy HFOs can be used to identify epilep-

tic areas. The surgical removal of HFO generating brain tissue correlated with a postsurgical seizure-free outcome. First studies indicate that HFOs might not only be visible on intracranial but also on surface EEG. This would allow for a much broader use of the biomarker. The present review will discuss which methodological requirements and improvement are needed to securely record and analyse HFOs. It will present clinical situations in which HFOs might be useful as well as point out the open questions which need to be answered prior to a routine clinical use of HFOs.

**Key words:** Ripple, fast ripple, high frequency oscillations, epilepsy surgery, spikes

### Oscillations à haute fréquence (80-500Hz): des marqueurs cliniques pour l'épileptologie ?

Pour les patients avec une épilepsie réfractaire aux traitements, le biomarquage fiable des aires épiléptogènes est d'une importance capitale. Par EEG intracrânien, il a maintenant été possible d'établir qu'en plus des pics interictaux et de l'analyse du foyer de la crise, les oscillations à haute fréquence (HFO) présentaient aussi un potentiel en tant que marqueurs des aires épiléptogènes. Ces HFO se situent dans une plage de fréquences comprises entre 80 et 500 Hz, elles ne durent que quelques millièmes de secondes et sont générées sur des parties infimes du cerveau. La modélisation animale a permis d'identifier un lien étroit entre HFO épiléptiques et épiléptogenèse. Les HFO peuvent également servir à identifier les aires épiléptogènes de patients avec une épilepsie rebelle au traitement. La résection des aires sur lesquelles des HFO sont générées corrèle avec la disparition post-opératoire des crises. Il existe déjà des études montrant que les HFO pourraient être des marqueurs EEG intéressants non seulement au niveau de l'EEG intracrânien, mais aussi dans l'EEG superficiel. Dans l'article, la discussion porte sur les conditions méthodologiques qui doivent être remplies pour assurer l'enregistrement et l'analyse fiables des HFO. On y présente également les différents modes d'intervention clinique possibles des HFO et les questions ouvertes qu'il s'agit de clarifier avant de vulgariser l'utilisation clinique des HFO.

**Mots clés :** ripple, fast ripple, oscillations à haute fréquence, chirurgie épileptique, pics

## Einleitung

Hochfrequenzoszillationen (HFO) zwischen 80-500Hz sind in den letzten Jahren zunehmend in den Blickwinkel von Epileptologen gerückt. Es besteht die Hoffnung, dass sie als sichere EEG-Marker für epileptogene Aktivität eingesetzt werden können. Früher war die klinische Analyse von EEGs vor allem auf die Berger-Frequenzen von 1-25 Hz begrenzt. Für Diagnosefindung und Verlaufskontrollen bei Epilepsie werden im EEG zum einen die Lokalisation und Häufigkeit von interiktalen epileptischen Potenzialen, zum Beispiel Spikes und Sharp Waves analysiert. Areale, die interiktale epileptische Potenziale zeigen, werden nach dem Modell zur prächirurgischen Diagnostik von Rosenow und Lüders [1] als irritative Zone bezeichnet. Weiterhin gilt die Identifikation der Anfallsursprungszone als Areal mit der ersten iktalen Aktivität im EEG als Goldstandard zur Eingrenzung epileptischer Areale in der prächirurgischen Epilepsiediagnostik. Trotz dieser beiden klar definierten Areale und immer besserer neurophysiologischer Diagnostik ist eine prognostische Abschätzung für den Spontanverlauf oder den postoperativen Verlauf einer Epilepsie bisher nur begrenzt möglich. Dies liegt auch an der schlechten Korrelation zwischen dem Auftreten von Spikes und der eigentlichen Krankheitsaktivität bzw. dem Auftreten von Anfällen. Das Ziel einer operativen Intervention ist die Entfernung nicht nur der Anfallsursprungszone, sondern aller potenziell epileptogenen Areale, auch epileptogene Zone genannt. Mit heutigen Mitteln ist eine Eingrenzung dieser Strukturen noch nicht möglich, und es besteht ein grosser Bedarf, neue EEG-Biomarker zu etablieren bzw. die bereits vorhandenen besser zu verstehen.

Detaillierte Berichte über die Verbindung von HFO und epileptogenen Arealen wurden erstmals in Studien mit Mikroelektroden beschrieben. Diese Mikroelektroden waren ursprünglich zusätzlich zu den klinischen Elektroden in die mesiotemporalen Strukturen von Patienten mit therapierefraktären Epilepsien implantiert worden, um physiologische Aktivität auf Einzelzellniveau analysieren zu können [2-4]. Bei den Analysen fiel auf, dass Oszillationen zwischen 250 und 500Hz, auch „fast ripple“ genannt, vor allem in Arealen gefunden wurden, die als Anfallsursprung identifiziert werden konnten. Kontralateral zu epileptogenen Arealen traten hingegen vermehrt „ripple“-Oszillationen zwischen 80-250Hz auf. Letztere wurden, angelehnt an die Ergebnisse aus Rattenstudien [5], als physiologisch und Teil von Gedächtnisprozessen interpretiert. Im Kainat-Tiermodell konnte im Folgenden ein klarer Zusammenhang zwischen dem Auftreten von „fast ripple“ und dem Entstehen von spontanen epileptischen Anfällen

gefunden werden [6]. Humane Daten zeigten neben dem klaren räumlichen Zusammenhang zwischen „fast ripple“ und der Anfallsursprungszone eine Korrelation zwischen „fast ripple“-Raten und dem Ausmass der läSIONellen hippokampalen Veränderungen wie Atrophie und Sklerose [7, 8]. Die Mikroelektrodenstudien waren alle aufgrund der spezifischen Struktur der Elektroden auf Aufzeichnungen aus mesiotemporalen Strukturen begrenzt. Da nachgewiesen werden konnte, dass „fast ripple“ über sehr kleinen Kortextarealen generiert werden [9], war es zweifelhaft, ob HFOs mit klinischen Standardelektroden, die bis zu 6000x grössere Oberflächen haben, aufgezeichnet werden können (**Abbildung 1/Elektrodentabelle**). Eine erste Studie zu iktalen HFOs konnte dann jedoch mit klinischen Elektroden Oszillationen zwischen 50-500Hz im Anfallsursprung nachweisen [10]. Da die Aufzeichnung mit Mikroelektroden aufgrund der notwendigen hohen Impedanzen spezielle Aufzeichngeräte benötigt und technisch aufwendig ist, entstand erst mit der Verwendung von klinischen Elektroden ein breites Interesse an HFOs als Biomarker. Als Konsequenz folgten zahlreiche Studien, die die Interaktion von HFOs mit den verschiedenen Arealen der prächirurgischen Diagnostik, wie der irritativen, der Anfallsursprungs- und der epileptogenen Zone untersuchten.

Elektrode	Grösse	Unterschied
Mikroelektrode	0.0012 mm <sup>2</sup>	
Adtech Makro	7 mm <sup>2</sup>	x6,000
Dixie Makro	5 mm <sup>2</sup>	x4,160
MNI Standard	0.8 mm <sup>2</sup>	x700
MNI Mikro	0.3 mm <sup>2</sup>	x84

**Abbildung 1:** Tabelle zur Übersicht über die verschiedenen durchschnittlichen Durchmesser der verschiedenen intrakraniell verwendeten Elektrodentypen, sowie der jeweiligen Grössenunterschiede. Dies soll eine Übersicht darstellen, viele Zentren verwenden aber auch speziell gefertigte Elektroden einzelner Hersteller, so dass diese Tabelle keinen Anspruch auf Vollständigkeit hat.

MNI = Montreal Neurological Institute

## HFO in der Anfallsursprungszone

Nachdem gezeigt werden konnte, dass Elektroden mit grossen Kontaktflächen HFOs aufzeichnen, wurde zunächst untersucht, ob HFOs vermehrt in der Anfallsursprungszone (= „seizure onset zone“, SOZ) auftreten und diese auch identifizieren können. Aus klinischen Gesichtspunkten ist dies eine wichtige Frage, da für die Bestimmung der Anfallsursprungsareale die

Auswertung mehrerer spontaner Anfälle notwendig ist. Die Häufigkeit von spontanen Anfällen ist meist dafür ausschlaggebend, wie lange intrakranielle implantierte Elektroden verbleiben müssen, bevor die Anfallsursprungszone, als Goldstandard für epileptogene Areale, eindeutig eingegrenzt werden kann. Da HFOs interiktal ausgewertet werden können und hierfür nur Abschnitte von wenigen Minuten benötigt werden, könnte ihre Analyse eine wesentliche Verkürzung der notwendigen Implantationsdauer bedeuten. Es zeigte sich, dass HFOs, sowohl „ripple“ als auch „fast ripple“, in signifikant höheren Raten in der Anfallsursprungszone auftreten als ausserhalb [11, 12]. Die Kanäle der Anfallsursprungszone konnten in retrospektiven Studien eindeutig mittels der Raten identifiziert werden [11, 13].

	Sensitivity for SOZ	Specificity for SOZ
Spike	33.5	86.2
Spike+R	29.4	94.6
Spike+FR	55.6	94.5
R	36.2	94.7
FR	51	94.5

Abbildung 2A: Die Tabelle (Teil A) zeigt die verschiedenen Spezifitäten und Sensitivitäten der einzelnen Marker für die Anfallsursprungszone. Besonders „fast ripple“ und Spikes mit „fast ripple“ haben eine hohe Spezifität für die Identifikation von Anfallsursprungsarealen.

## HFOs und interiktale epileptische Potenziale

Interiktale epileptische Potenziale, epileptische Spikes, sind einfach im EEG zu identifizieren und werden häufig als Marker für epileptische Aktivität verwendet. Sie sind jedoch nicht sehr spezifisch für die Anfallsursprungszone und es besteht vermutlich kein enger Zusammenhang zwischen der Aktivität der Epilepsie und dem Auftreten von epileptischen Spikes [14].

Urrestarazu und Kollegen beschäftigten sich erstmals detailliert mit den Interaktionen von Spikes und HFOs [15, 16]. Diese Fragestellung benötigt eine spezielle Auswertung, da Spikes und HFOs auf sehr unterschiedlichen Zeitachsen auftreten. Im gefilterten EEG, das zur Analyse von HFOs verwendet wird, sind epileptische Spikes nicht sichtbar und eine Auswertung in zwei unabhängigen EEG-Kopien ist daher notwendig. Hierbei konnten drei unterschiedliche Formen von HFOs unterschieden werden. Zunächst diejenigen, die zeitlich völlig unabhängig von Spikes auftraten, dann HFOs, die gleichzeitig mit Spikes auftraten und im ungefilterten EEG auf dem Spike sichtbar waren, und zuletzt HFOs, die gleichzeitig mit Spikes auftraten, aber nicht im ungefilterten EEG identifiziert werden konn-

ten [15]. Insgesamt treten zwischen 30-50 % der HFOs gemeinsam mit Spikes auf. Klinisch interessanter ist jedoch die Tatsache, dass Spikes ebenfalls mit und ohne HFOs auftreten können. Spikes mit HFOs zeigen eine stärkere Bindung an die Anfallsursprungszone und sind spezifischer für ihre Identifikation als Spikes ohne HFOs (Abbildung 2A). Eine Unterscheidung beider Spike-Formen ohne die Anwendung von Hochfrequenzfiltern ist jedoch nicht immer möglich (Abbildung 3). Durch die Kombination beider Marker für Epilepsie könnte es in Zukunft vielleicht möglich sein, die hohe Spezifität von HFOs für epileptogene Areale mit der einfacheren Analyse von Spikes zu kombinieren (Abbildung 2B). Ein Ansatz, dies zu verwirklichen, ist eine von Kobayashi publizierte Methode, bei der nicht einzelne HFO, sondern der hochfrequente Anteil von Spikes statistisch berechnet wird [17] (Abbildung 4). Diese Methode benötigt anstelle der zeitaufwendigen Einzelmarkierung von HFOs lediglich die Markierung von Spikes mit gleicher Topographie innerhalb eines Kanals. Es konnte nachgewiesen werden, dass die hoch-

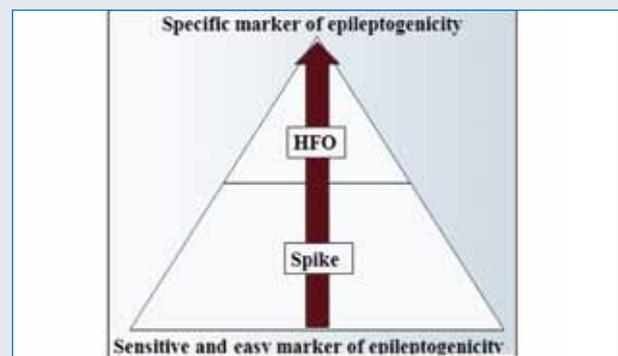


Abbildung 2B: Die Pyramide (Teil B) veranschaulicht, wie die Verwendung beider Marker zusammen zu einer verbesserten und erleichterten Identifikation der Anfallsursprungsareale führen kann, da Spikes einfacher zu markieren sind als HFO, HFOs jedoch deutlich spezifischer als Spikes.

requenten Anteile von Spikes in der Anfallsursprungszone signifikant höher waren als diejenigen von Spikes ausserhalb [18]. Vergleichsstudien dieser Methode mit der Markierung von Einzeloszillationen sind momentan in Arbeit.

## HFOs ausserhalb der Anfallsursprungszone

Es zeigte sich jedoch auch, dass das Auftreten von HFOs nicht einer Alles-oder-Nichts-Regel folgt. Vielmehr zeigten einige Areale HFOs, aber die mit den höchsten Raten lagen jeweils in der Anfallsursprungszone. Häufig fanden sich angrenzend oder separat weitere Hirnareale mit relativ hohen HFO-Raten. In diesen Fällen stellt sich die Frage, ob HFOs, ähnlich wie Spikes,

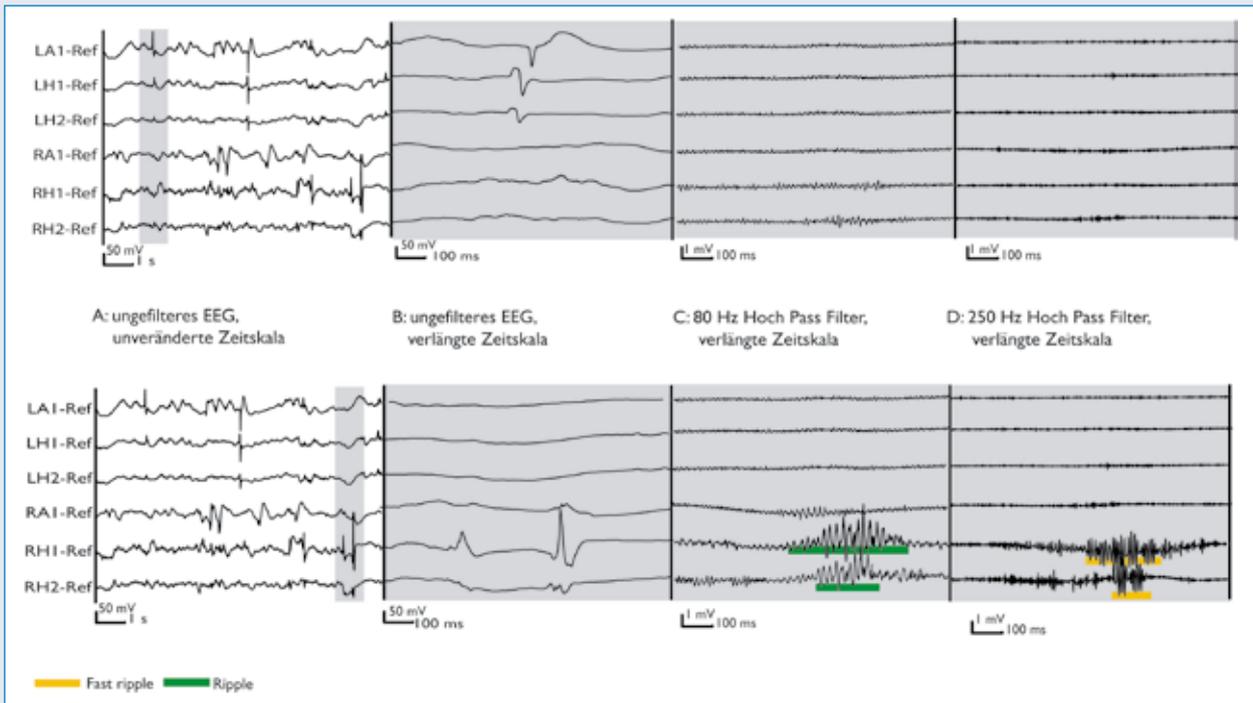


Abbildung 3: Intrakranielles EEG eines Patienten mit bilateralen interiktalen mesiotemporalen Spikes und einer Implantation in beide Hippocampi (R/L H) sowie beide Amygdala (R/L A). Anfälle wurde jedoch nur aus dem rechten Hippokampus beobachtet. Während die Spikes über beiden mesiotemporalen Regionen ungefiltert gleich aussahen, zeigten sich nach der Filterung nur über dem rechten Hippokampus Spikes, die mit HFOs assoziiert waren. Der graue Abschnitt in A ist in den Abschnitten B, C und D mit verlängerter Zeitachse dargestellt. Abschnitt C und D sind nach Anwendung eines Hochpassfilters mit deutlich höherer Verstärkung dargestellt. Abbildung nach Jacobs et al., 2009 mit Erlaubnis von Wiley and Sons.

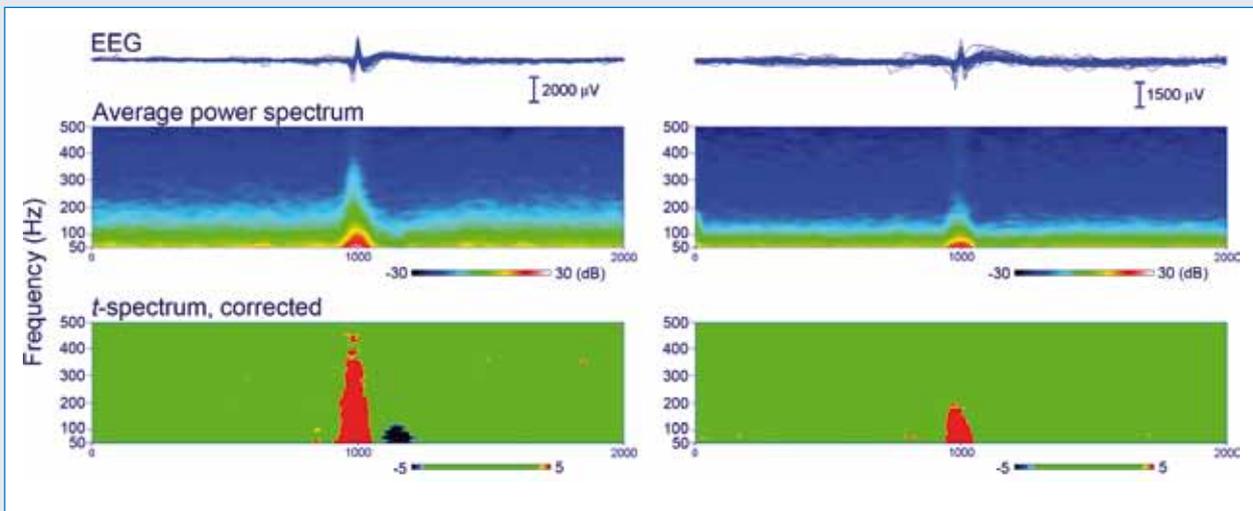


Abbildung 4: Hochfrequente Anteile während des epileptischen Spikes. Rechts Analyse der Spikes im Anfallsursprung, links Analyse von Spikes ausserhalb des Anfallsursprungs. Darstellung eines klassischen Zeit-Frequenz-Spektrums oben und unten einer statistischen Analyse der hochfrequenten EEG-Anteile während des Spikes im Vergleich zur EEG-Grundaktivität. Im Vergleich zu den Spikes ausserhalb des Anfallsursprungs zeigen die Spikes im Anfallsursprung klar einen höheren Anteil an „fast ripple“-Aktivität. Abbildung nach Kobayashi et al., 2009 mit Erlaubnis von Elsevier.

unspezifische Marker für epileptogene Areale sind, oder aber, ob HFOs potenziell epileptogene Areale ausserhalb der Anfallsursprungzone identifizieren können.

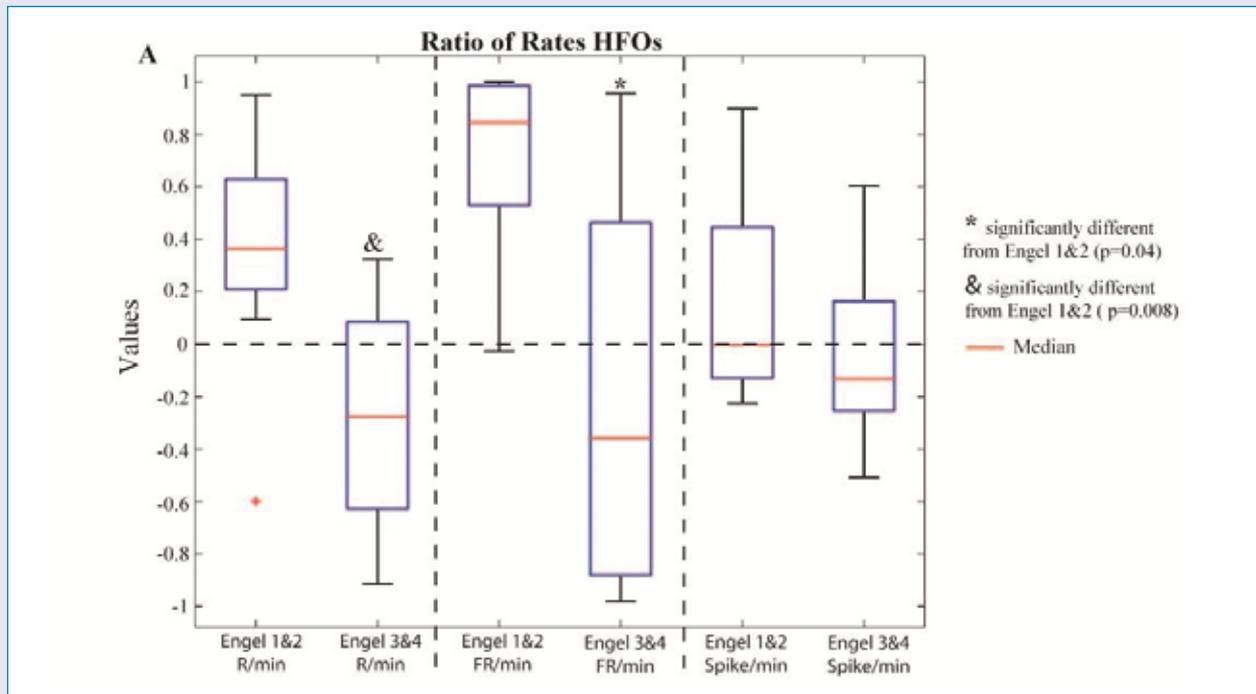
Eine Methode zur Identifikation von epileptogenen Arealen ist die elektrische Stimulation von Kortextare-

alen. Areale, über denen mit niedriger Amperezahl epileptische Potenziale, sogenannte „after-discharges“ oder aber auch epileptische Anfälle, ausgelöst werden, gelten als potenziell epileptogen und Gebiete mit einer niedrigen Anfallsschwelle. Auch bei der elektrischen

Stimulation werden häufig Gebiete ausserhalb der Anfallsursprungszone identifiziert, die besonders empfindlich für die Generierung epileptischer Aktivität sind, und deren Bedeutung schwer einzuschätzen ist. Eine Vergleichsstudie zwischen den Arealen, die auf Stimulation reagieren und denen, die HFOs generieren, zeigte eine signifikante negative Korrelation zwischen den HFO-Raten und der für die Auslösung einer epileptischen Antwort notwendigen Stromstärke [19]. Konkret bedeutet das, dass diejenigen Areale, über denen früh in der Stimulation eine epileptische Antwort auftrat, auch diejenigen waren, die viele HFOs zeigten. Interessanterweise gilt dies nicht nur für Gebiete innerhalb des Anfallsursprungs, sondern auch für Areale ausserhalb des Anfallsursprungs. Diese Beobachtung könnte also tatsächlich dafür sprechen, dass HFO zusätzliche epileptogene Areale identifizieren können.

Klinisch ist im Gesamtbild jedoch immer am interessantesten, ob die operative Entfernung von Arealen, die HFOs generieren, mit einer postoperativen Anfallsfreiheit korreliert. Diese Aussage kommt der Bestimmung der epileptogenen Zone am nächsten. Inzwischen gibt es einige Studien, die einen klaren Zusammenhang zwischen dem Anteil der entfernten Hirnareale mit HFOs und der postoperativen Anfallsfreiheit herstellen konnten (**Abbildung 5**) [20 - 23]. Alle bisher veröffentlichten Studien zeigten diese Korrelation, obwohl HFOs mit sehr unterschiedlichen intrakraniellen Elektroden von subduralen Streifen bis intrakraniellen

Tiefenelektroden aufgezeichnet wurden, die analysierten Frequenzbänder sich unterschieden und die Patientenpopulationen variierten. Selbst die Verwendung von kurzen intraoperativen Aufzeichnungen scheint für die Identifikation von „fast ripple“ ausreichend aussagekräftig [21]. Wu und Mitarbeiter präsentieren in ihrer Studie ausserdem einen Patienten, bei dem eine erste Operation nicht erfolgreich war. Nach der Nachresektion eines weiteren Hirnareals, über dem „fast ripple“ aufgezeichnet wurden, konnte eine Anfallsfreiheit erreicht werden. Prospektive Studien stehen zum momentanen Zeitpunkt noch aus. Hierfür wird es wichtig sein festzustellen, welche Areale mit HFOs relevant sind und welche nicht. Wie bereits oben erwähnt, wird es hierbei nicht nur um ein reines Identifizieren der Areale gehen, die hin und wieder HFOs zeigen, sondern vermutlich ist es wichtig, einen kritischen Schwellenwert für HFO-Raten zu bestimmen, ab dem eine Resektion notwendig ist. Akiyama und Mitarbeiter [22] haben hier einen ersten Vorschlag in ihrer retrospektiven Studie vorgestellt, bei der sie individuell für jeden Patienten einen Schwellenwert statistisch festgelegt haben und dadurch bestimmten, welche Areale als die mit höchster HFO-Aktivität eingestuft werden können. Diese Methodik benötigt jedoch eine genaue Evaluation in prospektiven Studien und grosse Vorsicht in anderen Patientengruppen. Ein ungelöstes Problem ist, dass HFO-Raten je nach Hirnregion sehr unterschiedlich sein können. Raten im Hippokampus und der Amygdala sind



**Abbildung 5:** Daten zur Korrelation der Entfernung von HFO-generierenden Arealen und der postoperativen Ergebnisse von 20 Patienten, die mit intrakraniellen Tiefenelektroden untersucht wurden. Bei Patienten mit gutem Ergebnis ([24] Engel 1&2) wurden signifikant höhere Anteile der HFO-generierenden Gebiete entfernt als bei Patienten mit schlechtem Ergebnis ([24] Engel 3&4). Dies trifft für „ripple“ und „fast ripple“, nicht jedoch für Spikes zu.

Abbildung nach Jacobs et al., 2010 mit Erlaubnis von Wiley and Sons.

prinzipiell höher als in den neokortikalen Arealen [11, 25]. Eine Schwellenwertfindung für Patienten mit Tiefelektroden sowohl im mesio-temporalen Bereich als auch zum Beispiel fronto-orbital kann daher fälschlicher Weise dazu führen, dass eine Anfallsursprungszone fronto-orbital übersehen und stattdessen im Hippokampus lokalisiert wird.

## HFO und Krankheitsaktivität

HFO-Raten sind nicht fixiert, sondern variieren je nach Vigilanzzustand. Für viele Studien wurden daher Tiefschlafdaten verwendet, da hier HFO-Raten generell am höchsten sind [26, 27]. Gleichzeitig konnte aber auch gezeigt werden, dass die Lokalisation von Anfallsursprungsarealen hierdurch unbeeinträchtigt ist, da die HFO-Raten zwar variieren, der relative Unterschied von HFOs in den verschiedenen Hirnregionen jedoch konstant bleibt. Es ist daher im Rahmen einer chronischen Aufzeichnung von intrakraniell EEG möglich, unabhängig von Tageszeit, Medikamentenstatus oder Anfallsfrequenz sicher diejenigen Hirnareale zu identifizieren, die in Bezug auf HFOs am aktivsten sind [27, 28]. Hierfür sind vermutlich 3-5 Minuten interiktales EEG ausreichend [29].

Die Variabilität von HFOs lässt jedoch hoffen, dass HFO-Raten nicht nur eine Lokalisationsinformation geben können, sondern gegebenenfalls auch das Ausmass der Krankheitsaktivität zu einem bestimmten Zeitpunkt, also das aktuelle epileptogene Potenzial des zugrunde liegenden Gewebes, widerspiegeln. Erste Hinweise hierauf lieferte die Arbeit von Zijlmans und Mitarbeitern, die HFO-Raten in den hintereinander liegenden Nächten während der Langzeitaufzeichnung analysierte. Hierbei zeigte sich, dass HFO-Raten signifikant ansteigen, wenn antiepileptische Medikamente reduziert werden (**Abbildung 6**). Im Gegensatz hierzu beeinflussten rezidivierende Anfälle das Auftreten von HFOs nicht.

Eine Korrelation zwischen Krankheitsaktivität und HFO-Raten fand sich auch bei Patienten mit verschiedenen Typen von Fokalen Kortikalen Dysplasien (FKD) [30]. In einer Gruppe von 21 untersuchten Patienten hatten Patienten mit Pathologien vom Typ Palmini 2a und b signifikant mehr Anfälle vor und während der EEG-Aufzeichnung als diejenigen mit FKD Typ 1a und b. Dies spiegelte sich auch in den Raten der HFOs wieder, die signifikant höher waren bei Patienten mit Grad 2 FKD. Wichtig erscheint, dass auch in dieser Studie die beschriebenen Ratenunterschiede die Lokalisation der Anfallsursprungszone nicht beeinflussten, da hier die Raten relativ gesehen immer am höchsten blieben. Dies passt zu der vorher gemachten Beobachtung, dass HFOs nicht primär vom Läsionstyp, sondern von der epileptischen Aktivität anhängig sind [12].

HFOs als Marker für Krankheitsaktivität haben natürlich eine weitreichende Bedeutung für die klinische

Beurteilung einer Epilepsie. Dies gilt noch mehr, falls es in Zukunft regelhaft möglich sein sollte, HFOs nicht nur im intrakraniellen EEG, sondern auch an der Oberfläche zu analysieren. Einen ersten Ausblick auf sich dann eröffnende Möglichkeiten stellt die Studie von Kobayashi und Mitarbeitern bei Patienten mit Rolandoepilepsie dar [31]. Spike assoziierte Veränderungen im „ripple“-Frequenzband korrelierten negativ mit der Zeit seit dem letzten Anfall der Patienten. Das heisst, Patienten mit einer gut kontrollierten Epilepsie hatten signifikant weniger Spike-assoziierte „ripple“ als solche mit persistierenden Anfällen unter Therapie.

## HFOs an der Oberfläche

Langzeitstudien, wie die soeben zitierte, sind natürlich nur dann denkbar, wenn HFOs nicht nur im intrakraniellen EEG, sondern auch an der Oberfläche sichtbar und auswertbar sind. Da der Schädel nicht, wie häufig angenommen, als Filter für hohe EEG-Frequenzen dient [32], ist dies auch prinzipiell denkbar. Skepsis bestand jedoch lange, da die Studien an Mikroelektroden klar darauf hinwiesen, dass Generatoren von HFOs sehr klein sind und hiermit vermutlich auch die Oberfläche, über der sie aufgezeichnet werden können. Bereits von epileptischen Spikes wissen wir, dass einige Zentimeter Kortex involviert sein müssen, um einen kortikalen Spike auch im Oberflächen-EEG sehen zu können [33, 34] und die Chancen, HFOs an der Oberfläche zu sehen, wurden daher eher skeptisch eingeschätzt. Hinzu kommt noch die Schwierigkeit, spontan auftretende HFOs sicher von Muskelartefakten, die im gleichen Frequenzbereich auftreten, zu unterscheiden. Im MEG gab es jedoch Hinweise, dass epileptische Gamma-Oszillationen über der Anfallsursprungszone sichtbar sein können [35]. Wu und Mitarbeiter beschrieben erstmals, dass Oszillationen oberhalb von 100Hz ein prognostischer Marker bei Kindern mit West-Syndrom sein könnten [21].

Um das Problem der Muskelkontamination zu vermeiden und hochfrequente Aktivität schneller zu analysieren, verwendeten Kobayashi und Mitarbeiter keine Analyse einzelner HFOs, sondern eine Technik zur Mittelung der hochfrequenten Anteile der Zeit-Frequenzspektra von Spikes. Hierdurch konnten sie nicht nur in verschiedenen pädiatrischen Patientengruppen HFOs auf Spikes nachweisen [36, 37, 31], sondern in einem Anfall Frequenzen bis zu 800 Hz direkt im Anfallsursprung identifizieren [38].

Im letzten Jahr konnten dann im Oberflächen-EEG „ripple“-Oszillationen in Routineuntersuchungen bei Epilepsiepatienten nachgewiesen werden [39]. Sie zeigen eine erstaunliche Ähnlichkeit zu Oszillationen im intrakraniellen EEG. Auch hier können „ripple“ innerhalb und ausserhalb von Spikes auftreten, und einige sind auf dem ungefilterten Spike erkennbar. Wie bei intrakraniell aufgezeichneten „ripple“, zeigen „ripple“

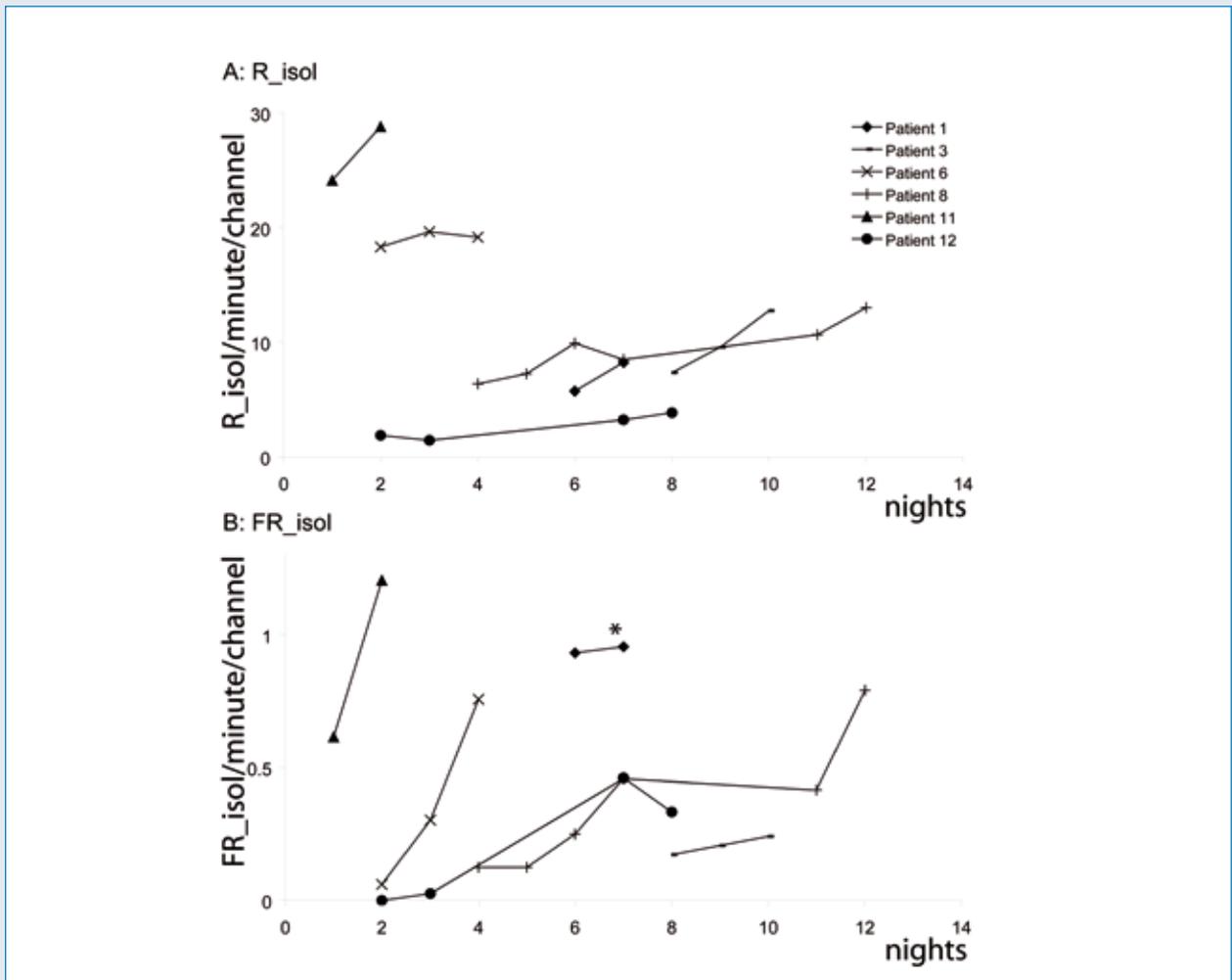


Abbildung 6: Darstellung der Veränderung der „ripple“-Raten (oben) bzw. der „fast ripple“-Raten (unten) im Verlauf während der chronischen Ableitung des intrakraniellen EEG und während des langsamen Absetzens der antiepileptischen Medikation. Es wurden nur Nächte und Patienten eingeschlossen, bei denen keine Anfälle während des Zeitraums als Einflussfaktoren auftraten. Raten der HFOs nahmen nach der Reduktion der Medikamente über die Nächte hinweg signifikant zu.

Abbildung nach Zijlmans et al., 2009 mit Erlaubnis von Wolters Kluwer.

an der Oberfläche eine höhere Spezifität für den Anfallsursprung (Abbildung 7). Insgesamt sind sie jedoch mit einer Rate um die 0,5/Minute sehr viel seltener als intrakranielle Oszillationen. Es stellt sich die Frage,

welche der intrakraniell dargestellten HFOs auch an der Oberfläche sichtbar sind. Hierfür werden ausführliche Studien notwendig sein. Erste Ergebnisse sind jedoch überraschend: Nicht eine flächige Ausbreitung

	Sensitivity for SOZ	Specificity for SOZ
Spike	100%	30%
Gamma	82%	68%
Ripple	48%	98%

Abbildung 7: Tabelle erstellt nach den Ergebnissen von Andrade-Valenca et al., 2011. An der Oberfläche gemessene „ripple“ zeigen eine hohe Spezifität für epileptogene Areale.

oder Propagation, sondern das synchronisierte Auftreten von Einzeloszillationen auf verschiedenen kleinen und entfernt gelegenen Generatoren scheint zu einem sichtbaren Oberflächen-HFO zu führen [40].

### Sind wir bereit für den klinischen Einsatz?

Die Identifikation von HFOs in Makroelektroden, ja sogar Oberflächenkontakten, und die Entwicklung

aus, dass die im Hippokampus beobachteten „ripple“-Oszillationen, wie aus Rattenstudien bekannt, physiologische Oszillationen im Rahmen der Gedächtniskonsolidierung sind [7, 41]. Nur „fast ripple“ wurden als pathologisch eingestuft. Diese Einschätzungen lassen sich jedoch nicht ungeprüft auf neokortikale Areale übertragen und liessen sich auch für die mesiotemporalen Strukturen mit Makroelektroden nicht bestätigen. In ihrer Übersichtsarbeit „High-frequency oscillations: what is normal and what is not?“ kommen Engel

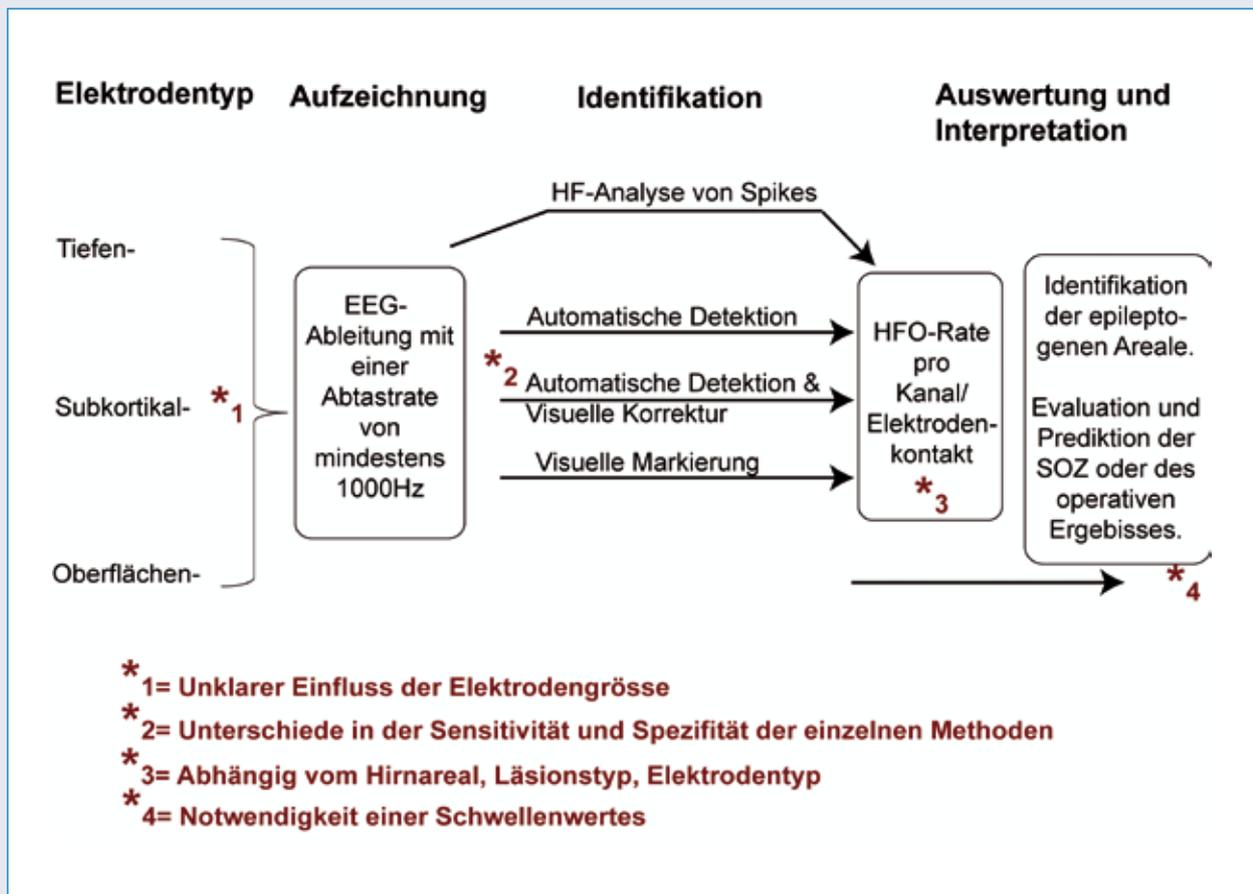


Abbildung 8: Überblick über die bisher verwendeten Methoden zur Identifikation und Auswertung von HFOs. Rote Nummern zeigen diejenigen Schritte, bei denen bisher Unsicherheiten bei der Auswertung bestehen, die dringend geklärt werden müssen, bevor HFOs als EEG-Marker eine breite Anwendung finden.

von immer neuen Verstärkern, die ohne Probleme mit Abtastraten zwischen 2000-10000Hz aufzeichnen, verleitet dazu, HFOs für den breiten klinischen Einsatz zu empfehlen. **Abbildung 8** gibt einen Überblick über die hierbei möglichen methodischen Ansätze. Aus Sicht der Autorin sind die momentan verwendeten Auswertungsmethoden und das Wissen über HFOs jedoch weit von einem klinischen Routineeinsatz der HFOs als EEG-Marker entfernt.

Eine wichtige Herausforderung für prospektive Studien und die klinische Auswertung ist die sichere Unterscheidung von physiologischen und epileptischen HFOs. Die ersten Mikroelektrodenstudien gingen davon

und Mitarbeiter klar zu dem Schluss, dass eine reine Frequenzanalyse nicht ausreichend sein wird, um physiologische und pathologische HFOs voneinander abzugrenzen [42]. Jede Studie am Patienten analysiert daher vermutlich eine Mischung aus physiologischen und pathologischen Oszillationen. Ein Weg, dies zu umgehen, mag die alleinige Analyse von Spike-gekoppelten HFOs sein. Andere Unterscheidungskriterien sind in Bearbeitung. Bis dieses Problem jedoch gelöst ist, sollte die Interpretation von HFOs mit grosser Vorsicht erfolgen.

Die Unterscheidung von pathologischen und physiologischen HFOs ist auch daher schwierig, da bis-

her grosse Teile der Entstehungsmechanismen dieser schnellen Oszillationen ungeklärt sind [43]. Vor allem ist auch unklar, ob diejenigen Oszillationen, die mit Mikrokontakten aufgezeichnet wurden, denen entsprechen, die mit Makrokontakten aufgezeichnet wurden und an der Oberfläche sichtbar sind. Es ist umstritten, ob Mikro- und Makroelektroden die gleiche Anzahl und Art von HFOs aufzeichnen, subdurale Elektroden sind immerhin 6000x grösser als Mikroelektroden [44, 45]. Falls Makrokontakte nur weniger HFOs identifizieren, könnte dies sowohl ein positiver Filtereffekt sein, der die besonders pathologisch relevanten Ereignisse darstellt oder auch eine sich negativ auswirkende zu niedrige Auflösung widerspiegeln.

Zuletzt soll auch die bereits weiter oben im Artikel erwähnte Festlegung eines Schwellenwertes noch einmal diskutiert werden. In einem prospektiven Einsatz der HFOs wird der Epileptologe entscheiden müssen, welche Hirnareale vermutlich epileptogen sind und daher operativ entfernt werden sollen, oder aber auch, welche Rate von HFOs prognostisch bei einem Patienten ungünstig ist bzw. welche nicht. HFO-Raten sind jedoch vermutlich in hohem Masse abhängig von der verwendeten Elektrode, Identifikationsmethoden, dem betroffenen Hirnareal und gegebenenfalls auch von der zugrunde liegenden Pathologie. Es wird daher eine Herausforderung für viele kommende Studien sein herauszufinden, wie möglichst allgemein verwendbare Schwellenwerte festgelegt werden können, um HFOs mit der richtigen Sensitivität und Spezifität für epileptogene Areale einsetzen zu können.

## Schlussfolgerung

Im Mai 2011 fand der erste internationale Workshop zum Thema HFOs in Montreal statt. Hier wurden drei wichtige Empfehlungen für die klinische Anwendung von HFOs ausgesprochen. Zur Vereinheitlichung der Diskussion und Vergleichbarkeit der Ergebnisse sollte bei allen Publikationen das analysierte Frequenzband im Titel und Abstrakt angegeben werden, denn wer von HFOs spricht, könnte alles im Frequenzband zwischen 80-1000Hz meinen. Weiterhin ist eine alleinige Frequenzanalyse nicht ausreichend, um pathologische und physiologische Oszillationen zu unterscheiden und alle Studien sollten bei der Interpretation der gefundenen Oszillationen die notwendige Vorsicht walten lassen. Als nächster Schritt in der Evaluation von HFOs werden multizentrisch angelegte, kontrollierte, prospektive Studien unter Verwendung von verschiedenen Aufzeichnungs- und Analyse-Methoden und differenzierten statistischen Verfahren angesehen.

Zusammenfassend sind HFOs spannende und vielversprechende Marker für epileptische Areale. Mit der Analyse von wenigen Minuten eines EEGs können sie die Anfallsursprungszone nicht nur spezifischer, sondern auch schneller identifizieren als herkömmliche

EEG-Marker. Sie haben daher das Potenzial, ein neuer wichtiger Bestandteil der prächirurgischen Evaluation von theapierefraktären Epilepsiepatienten zu werden. Darüber hinaus könnte vielleicht durch die nicht invasive Aufzeichnung auch die weit grössere Patientengruppe mit behandelbaren Epilepsien durch die Verwendung von HFOs als prognostischen Marker profitieren. Zum momentanen Zeitpunkt lernen wir jedoch jede Woche noch neue Aspekte dieser kurzen, schnellen Oszillationen kennen, und dies sollte als klares Zeichen dafür gewertet werden, dass unser Wissen noch nicht weit genug für eine unkritische klinische Anwendung ist.

## Referenzen

1. Rosenow F, Luders H. Presurgical evaluation of epilepsy. *Brain* 2001; 124: 1683-1700
2. Staba RJ, Wilson CL, Bragin A et al. Quantitative analysis of high-frequency oscillations (80-500 Hz) recorded in human epileptic hippocampus and entorhinal cortex. *J Neurophysiol* 2002; 88: 1743-1752
3. Bragin A, Engel J Jr, Wilson CL et al. High-frequency oscillations in human brain. *Hippocampus* 1999; 9: 137-142
4. Bragin A, Engel J Jr, Wilson CL et al. Hippocampal and entorhinal cortex high-frequency oscillations (100-500 Hz) in human epileptic brain and in kainic acid-treated rats with chronic seizures. *Epilepsia* 1999; 40: 127-137
5. Draguhn A, Traub RD, Bibbig A, Schmitz D. Ripple (approximately 200 Hz) oscillations in temporal structures. *J Clin Neurophysiol* 2000; 17: 361-376
6. Bragin A, Wilson CL, Almajano J et al. High-frequency oscillations after status epilepticus: epileptogenesis and seizure genesis. *Epilepsia* 2004; 45: 1017-1023
7. Staba RJ, Frighetto L, Behnke EJ et al. Increased fast ripple to ripple ratios correlate with reduced hippocampal volumes and neuron loss in temporal lobe epilepsy patients. *Epilepsia* 2007; 48: 2130-2138
8. Ogren JA, Wilson CL, Bragin A et al. Three-dimensional surface maps link local atrophy and fast ripples in human epileptic hippocampus. *Ann Neurol* 2009; 66: 783-791
9. Bragin A, Mody I, Wilson CL, Engel J Jr. Local generation of fast ripples in epileptic brain. *J Neurosci* 2002; 22: 2012-2021
10. Jirsch JD, Urrestarazu E, LeVan P et al. High-frequency oscillations during human focal seizures. *Brain* 2006; 129: 1593-1608
11. Jacobs J, LeVan P, Chander R et al. Interictal high-frequency oscillations (80-500 Hz) are an indicator of seizure onset areas independent of spikes in the human epileptic brain. *Epilepsia* 2008; 49: 1893-1907
12. Jacobs J, LeVan P, Chatillon CE et al. High frequency oscillations in intracranial EEGs mark epileptogenicity rather than lesion type. *Brain* 2009; 132: 1022-1037
13. Crepon B, Navarro V, Hasboun D et al. Mapping interictal oscillations greater than 200 Hz recorded with intracranial macroelectrodes in human epilepsy. *Brain* 2010; 133: 33-45
14. Hufnagel A, Dumpelmann M, Zentner J et al. Clinical relevance of quantified intracranial interictal spike activity in presurgical evaluation of epilepsy. *Epilepsia* 2000; 41: 467-478
15. Urrestarazu E, Chander R, Dubeau F, Gotman J. Interictal high-frequency oscillations (100-500 Hz) in the intracerebral EEG of epileptic patients.

- Brain* 2007; 130: 2354-2366
16. Urrestarazu E, Jirsch JD, LeVan P et al. High-frequency intracerebral EEG activity (100-500 Hz) following interictal spikes. *Epilepsia* 2006; 47: 1465-1476
  17. Kobayashi K, Jacobs J, Gotman J. Detection of changes of high-frequency activity by statistical time-frequency analysis in epileptic spikes. *Clin Neurophysiol* 2009; 120: 1070-1077
  18. Jacobs J, Kerber K, Levan P et al. Occurrence of high frequency oscillations depends on pathology in patients with focal cortical dysplasia. *Epilepsy Currents* 2011; 11(S 1): 1 (Abst. 2.035)
  19. Jacobs J, Zijlmans M, Zelmann R et al. Value of electrical stimulation and high frequency oscillations (80-500 Hz) in identifying epileptogenic areas during intracranial EEG recordings. *Epilepsia* 2010; 51: 573-582
  20. Jacobs J, Zijlmans M, Zelmann R et al. High-frequency electroencephalographic oscillations correlate with outcome of epilepsy surgery. *Ann Neurol* 2010; 67: 209-220
  21. Wu JY, Sankar R, Lerner JT et al. Removing interictal fast ripples on electrocorticography linked with seizure freedom in children. *Neurology* 2010; 75: 1686-1694
  22. Akiyama T, McCoy B, Go CY et al. Focal resection of fast ripples on extraoperative intracranial EEG improves seizure outcome in pediatric epilepsy. *Epilepsia* 2011; 52: 1802-1811
  23. Ochi A, Otsubo H, Donner EJ et al. Dynamic changes of ictal high-frequency oscillations in neocortical epilepsy: using multiple band frequency analysis. *Epilepsia* 2007; 48: 286-296
  24. Engel J Jr. Update on surgical treatment of the epilepsies. Summary of the Second Palm Desert Conference on the Surgical Treatment of the Epilepsies 1992. *Neurology* 1993; 43: 1612-1617
  25. Jacobs J, LeVan P, Dubeau F, Gotman J. Generation of high frequency oscillations (80-500 Hz) in different anatomical structures and their relation to the seizure onset zone. 2009; 120: e29-e30
  26. Staba RJ, Wilson CL, Bragin A et al. High-frequency oscillations recorded in human medial temporal lobe during sleep. *Ann Neurol* 2004; 56: 108-115
  27. Bagshaw AP, Jacobs J, LeVan P et al. Effect of sleep stage on interictal high-frequency oscillations recorded from depth macroelectrodes in patients with focal epilepsy. *Epilepsia* 2009; 50: 617-628
  28. Zijlmans M, Jacobs J, Zelmann R et al. High-frequency oscillations mirror disease activity in patients with epilepsy. *Neurology* 2009; 72: 979-986
  29. Zelmann R, Zijlmans M, Jacobs J et al. Improving the identification of high frequency oscillations. *Clin Neurophysiol* 2009; 120: 1457-1464
  30. Jacobs J, Kobayashi K, Gotman J. High-frequency changes during interictal spikes detected by time-frequency analysis. *Clin Neurophysiol* 2011; 122: 32-42
  31. Kobayashi K, Yoshinaga H, Toda Y et al. High-frequency oscillations in idiopathic partial epilepsy of childhood. *Epilepsia* 2011; 52: 1812-1819
  32. Oostendorp TF, Delbeke J, Stegeman DF. The conductivity of the human skull: results of in vivo and in vitro measurements. *IEEE Trans Biomed Eng* 2000; 47: 1487-1492
  33. Tao JX, Ray A, Hawes-Ebersole S, Ebersole JS. Intracranial EEG substrates of scalp EEG interictal spikes. *Epilepsia* 2005; 46: 669-676
  34. Tao JX, Baldwin M, Hawes-Ebersole S, Ebersole JS. Cortical substrates of scalp EEG epileptiform discharges. *J Clin Neurophysiol* 2007; 24: 96-100
  35. Rampp S, Kaltenhauser M, Weigel D et al. MEG correlates of epileptic high gamma oscillations in invasive EEG. *Epilepsia* 2010; 51: 1638-1642
  36. Kobayashi K, Oka M, Akiyama T et al. Very fast rhythmic activity on scalp EEG associated with epileptic spasms. *Epilepsia* 2004; 45: 488-496
  37. Kobayashi K, Watanabe Y, Inoue T et al. Scalp-recorded high-frequency oscillations in childhood sleep-induced electrical status epilepticus. *Epilepsia* 2010; 51: 2190-2194
  38. Kobayashi K, Agari T, Oka M et al. Detection of seizure-associated high-frequency oscillations above 500Hz. *Epilepsy Res* 2010; 88: 139-144
  39. Andrade-Valenca LP, Dubeau F, Mari F et al. Interictal scalp fast oscillations as a marker of the seizure onset zone. *Neurology* 2011; 77: 524-531
  40. Zelmann R, Kerber K, Schulze-Bonhage A et al. Scalp correlates of intracranial high frequency oscillations in epilepsy. *Epilepsy Currents* 2012; 12: 178 (Abst: 2130)
  41. Bragin A, Wilson CL, Staba RJ et al. Interictal high-frequency oscillations (80-500 Hz) in the human epileptic brain: entorhinal cortex. *Ann Neurol* 2002; 52: 407-415
  42. Engel J Jr, Bragin A, Staba R, Mody I. High-frequency oscillations: what is normal and what is not? *Epilepsia* 2009; 50: 598-604
  43. Kohling R, Staley K. Network mechanisms for fast ripple activity in epileptic tissue. *Epilepsy Res* 2011; 97: 318-323
  44. Worrell GA, Gardner AB, Stead SM et al. High-frequency oscillations in human temporal lobe: simultaneous microwire and clinical macroelectrode recordings. *Brain* 2008; 131: 928-937
  45. Chatillon CE, Zelmann R, Bortel A et al. Smaller size of macroelectrodes does not improve HFO detection in intracerebral EEG recordings of the chronic epileptic rat. *Clin Neurophysiol* 2009; 50: 18-19

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### Summary

Over the past few decades, diverse brain imaging techniques have been applied in different areas of experimental psychology and neuroscience, and have begun to provide unprecedented windows on the functional and the structural anatomy of the human brain. Recent technological innovations have achieved to convert conventional electrophysiological methods (e.g. electroencephalogram or EEG) into modern functional brain imaging procedures (i.e. electric source imaging or ESI); allowing neuroscientists to measure the spatial and temporal dynamics of the brain.

In patients with drug-resistant epilepsy who are candidates for surgery, non-invasive functional imaging methods are helpful in guiding placement of surgical resections or invasive EEG recordings. ESI consists in a non-invasive recording of the electrical potential field on the scalp while using dense array EEG (up to 256 channels), which allows estimating intra-cerebral electric sources. Nowadays, ESI became an accessible technique mainly due to the increase in computational power and the appearance of user-friendly sophisticated analysis software. Despite the large amount of literature supporting the validity of ESI in terms of localization, the introduction of this technique into clinical routine has been rather slow. In this review we intend to tackle the theoretical aspects, practical procedures and ESI clinical studies; in addition, we will compare with other well established imaging tools used in presurgical evaluation of epilepsy workup.

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**Keywords:** Multichannel EEG, EEG source imaging (ESI), long-term EEG monitoring, epilepsy surgery, presurgical evaluation

### Nicht-invasive Lokalisierung von fokaler epileptischer Aktivität mittels elektrischer Bildgebung

In den letzten Jahrzehnten wurden mehrere Hirnbildgebungsverfahren in verschiedenen Bereichen der experimentellen Psychologie und Neurowissen-

schaften angewandt, die uns ein noch nie dagewesenes Fenster in die funktionelle und strukturelle Anatomie des menschlichen Gehirns gegeben haben. Technische Innovationen führten zu einer Umwandlung von konventionellen elektrophysiologischen Methoden (hier: Elektroenzephalogramm oder EEG) in moderne funktionelle Bildgebung (das heisst elektrische Quellenlokalisation oder ESI), die den Neurowissenschaftlern erlaubte, die räumliche und zeitliche Dynamik des Gehirns zu messen.

In Patienten mit Medikamenten-resistenter Epilepsie, die chirurgische Kandidaten sind, zeigten sich nicht-invasive funktionelle Bildgebungsverfahren sehr hilfreich, den Resektionsort oder den Ort der Platzierung der intrakraniellen Elektroden zu bestimmen. ESI besteht aus dem nicht-invasiven Aufnehmen des elektrischen Potenzialfelds auf dem Skalp mit hochauflösenden EEG (das heisst bis zu 256 Elektroden), was die Schätzung der intrazerebralen elektrischen Quelle erlaubt. Heutzutage ist ESI eine relativ zugängliche Technik, dank höherer Computerleistung und benutzerfreundlicher Analyse-Software. Trotz vieler Studien, die die Validität von ESI bezüglich Fokuslokalisation zeigen konnten, ist die klinische Einführung eher langsam. In dieser Zusammenschau umreissen wir die theoretischen und praktischen Aspekte sowie die klinischen ESI-Studien; ausserdem werden wir ESI mit anderen etablierten Bildgebungsverfahren, die in der prächirurgischen Evaluation angewandt werden, vergleichen.

**Schlüsselwörter:** EEG-Quellenlokalisation, Epilepsiechirurgie, Bildgebung

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## Localisation non invasive des réseaux épileptiques au moyen de l'imagerie de source électrique : état de l'art

Ces dernières années, les efforts dans la recherche neuroscientifique ont permis le développement de techniques modernes permettant l'exploration avancée du fonctionnement et de l'anatomie du cerveau. Des innovations technologiques récentes, ont réussi à convertir les méthodes neurophysiologiques conventionnelles (électroencéphalogramme) en techniques d'imagerie fonctionnelle (imagerie de source électrique). Cette évolution nous permet d'étudier l'activité cérébrale avec des résolutions spatiales et temporelles accrues.

Les techniques d'imagerie fonctionnelles non invasives sont utiles pour localiser la zone épileptogène chez des patients avec une épilepsie pharmaco-résistante et candidats à une résection chirurgicale de leur foyer épileptique. L'imagerie de source est basée sur des enregistrements électroencéphalographiques multicanaux (jusqu'à 256 électrodes), nous permettant d'obtenir une configuration topographique du champ électrique de surface et d'estimer les sources électriques sous-jacentes dans le cerveau individuel. Grâce à des améliorations sur le plan computationnel ainsi qu'au développement de logiciels plus abordables pour les utilisateurs, l'imagerie de source est devenue une technique accessible au monde médical clinique. Néanmoins, malgré une vaste littérature scientifique validant cette technique en termes de localisation, son utilisation en tant qu'examen de routine dans le domaine de l'épilepsie reste limitée.

Dans ce contexte, les aspects théoriques et pratiques de l'imagerie de source seront présentés. De plus, nous allons citer les différentes études cliniques qui ont utilisé cette technique, et nous allons la comparer avec des nouvelles méthodes d'imagerie fonctionnelle et structurelle.

**Mots-clés :** Imagerie de source EEG, chirurgie de l'épilepsie, EEG multicanaux

### Introduction

Epilepsy is a neurological disorder with a reported overall incidence of 50/100,000 cases per year and a prevalence of 4-10/1000 persons in industrialized countries [1]. In most cases, seizure appearance can be controlled by antiepileptic medication. However, approximately 1/4 to 1/3 of epileptic patients suffer from medically-refractory seizures [2]. Insufficient control of epileptic seizures and drug toxicity burden (linked to multiple medication and elevated dose), are related to an increase in morbidity and, moreover, have a large impact on patient's quality of life and disease-related costs [3].

Epilepsy surgery in eligible candidates might sub-

stantially reduce or eliminate seizure appearance at a rate of ~60% [4]. The main aim of epilepsy surgery is to delimit the resection margins of the epileptogenic area with preservation of the so-called "eloquent cortex" (i.e. cortical region vital for a certain neurological function).

Presurgical workup comprises several non-invasive techniques such as long-term scalp video-electroencephalogram (EEG) monitoring, invasive subdural EEG recordings (sEEG), high-resolution magnetic resonance imaging (MRI), positron emission tomography (PET), ictal and interictal single photon emission computed tomography (SPECT), subtraction of the two SPECT modalities coregistered to MRI (SISCOM) and quantitative MRI analysis which is recently gaining popularity [5]. The neurologist's capacity to determine the epileptogenic zone is based on sensitivities and specificities of the aforementioned methods. These techniques yield a ~50-80% correct localization of the epileptic area as validated by surgery and/or intracranial EEG, varying according to the presence or absence of visible structural lesion [6, 7]. Regarding more practical aspects, the use of brain imaging tools requires a certain degree of cooperation and understanding. Many patients either in pediatric age and/or with moderate-to-severe cognitive impairment might need sedation in order to accomplish these examinations, which imply an additional safety risk. In this sense, non-invasive and safer tools for mapping epileptic activity in the alert subject are needed.

These requirements are fulfilled by EEG source imaging (ESI), a technique based on non-invasive scalp EEG recorded with multiple electrodes, which allow estimating the underlying electric sources of the brain. This modern tool can be applied to study the dynamics of the epileptic network with high temporal resolution, enhancing our knowledge on the neurophysiological mechanisms of seizure disorders.

This review is intended to describe the current of the role of ESI in presurgical evaluation workup, ranging from its methodological background to the latest clinical studies, as well as its concordance with other brain imaging techniques.

### EEG in presurgical evaluation of epilepsy

Despite current technological innovations, interictal and ictal EEG recorded continuously during several days (i.e. long term monitoring), by either scalp electrodes or subdural grids, remain the gold standard in presurgical evaluation of drug-resistant epileptic patients.

During the period while the subject is being monitored a large amount of EEG, during awake and sleep stages, are digitally recorded. Subsequently, analysis is performed on the basis of visual detection of the spatial distribution and amplitude maxima of different EEG abnormalities (i.e. sharp waves and spikes). In

terms of localization, this type of analysis can be considered quite valuable; however, it only provides partial information available on the EEG signal and, furthermore, it is operator-dependant [8].

Since the 50's, sEEG play an essential role in localization precision, allowing ictal recordings to be performed without skull attenuation [9]. Nevertheless, this tool is highly invasive, thus, implying a certain degree of post-operative risk [10]; and confined to near-by cortex since it records signals originated from a limited circumference of neighboring tissue [11].

In order to avoid these technical limitations and potential risks, several epilepsy centers are currently analyzing EEG signals with modern non-invasive signal processing tools. EEG Source Imaging (ESI) is a technique, based on the recording of the electrical potential field on the scalp using multichannel EEG, which allows for the 3D reconstruction of the electric active areas in the brain. Subsequently, we will explain how we carry out multichannel EEG data acquisition and pre-processing in our presurgical unit. In addition, we will expose the theoretical framework underlying ESI and its current clinical applications. Finally, we will contrast this technique with other non-invasive tools.

### ESI of interictal epileptiform activity: practical procedures and underlying theoretical concepts

During the past few years, enormous progress has been made in the neuroscience laboratories concerning the recording analysis and interpretation of EEG. Nowadays, electrical signals are recorded from a large array of electrodes distributed all over the scalp (up to 256 channels). These methodological and practical improvements have encouraged the application of multichannel recordings and analysis, by means of ESI, in the epilepsy domain [12-14] (**Figure 1a**).

Interictal epileptiform activity (i.e. spikes) of similar localisation and morphology are visually detected and averaged and a potential map is obtained for each time point (**Figure 1b**). The EEG map at the 50% rising phase of the averaged interictal activity is selected for further source localization. It has been argued that the primary focus is more consistently localized whilst using the rising phase rather than interictal epileptogenic discharge peak, which already involves areas of propagation [15, 16].

Using spatial configuration of the scalp's potentials, with sophisticated inverse solution algorithms, allow estimating the underlying electric sources in the realistic brain [17] (**Figure 1c**); transforming the recording of these signals into a functional brain imaging method. These techniques have to face mathematical challenges referred to as the forward and the inverse problem.

The dilemma of determining the source locations which are responsible for the measured potentials at the EEG electrodes is known as the inverse problem

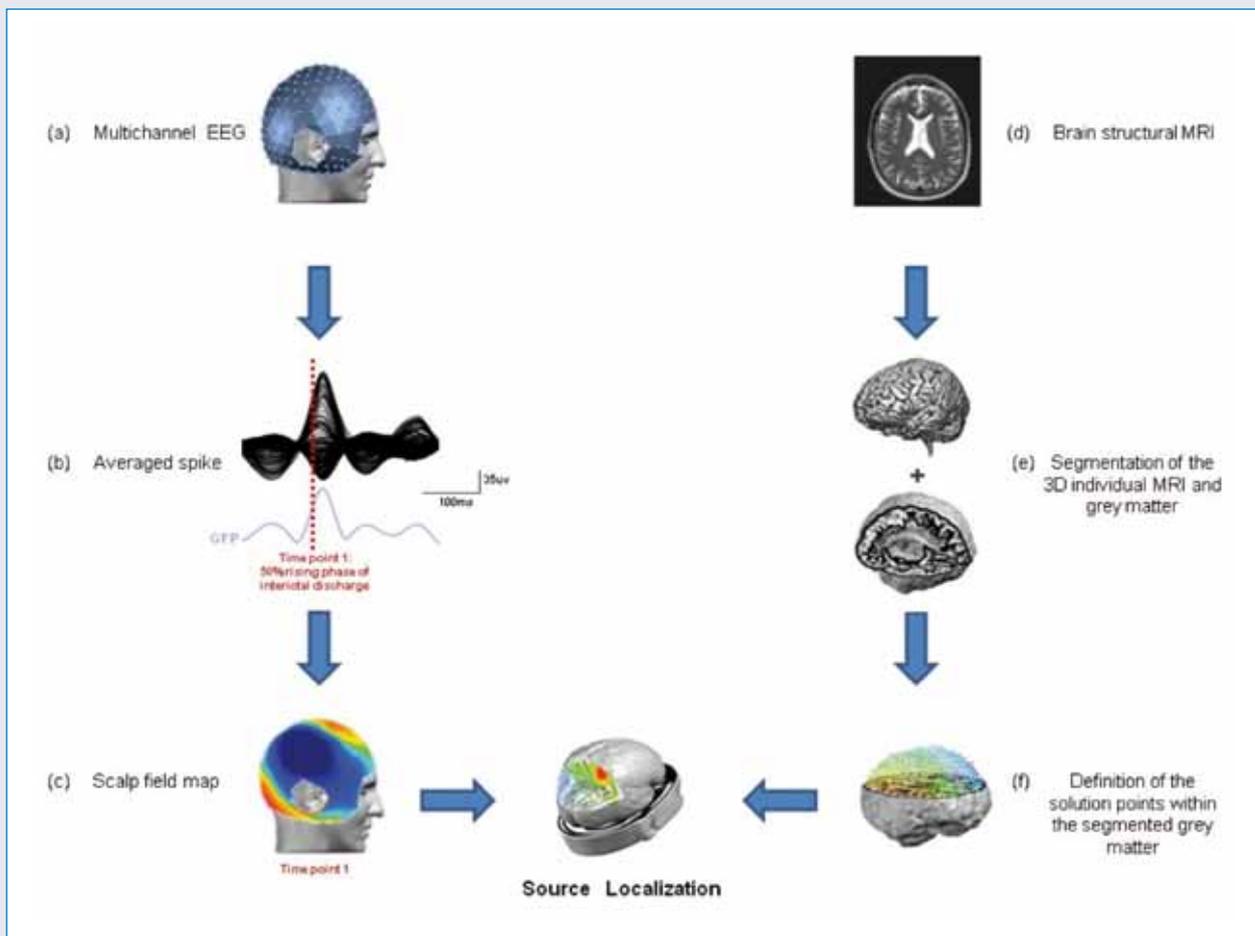
[18]. For any set of measurements or recording sensors outside the head, there are infinite current sources in the brain that model the recorded data (for review see [19]). Two different groups of algorithms, which are capable of estimating the sources of scalp activity, have been described in the literature: simple dipole estimations (i.e. continuous dipole analysis [20]; multiple distributed current dipole [21]) and, more recently developed, three-dimensional current density distribution methods (for reviews see [22]).

All these techniques are based on a model of the propagation of electrical activity through different conductivity values of the interfaces such as brain, skull and scalp: the forward model, expressed as the lead field matrix [23-25]. The inversion of this matrix by means of sophisticated algorithms provides the so-called "source localization". This would mean that for each time point within the spike wave complex, inverse solution calculation is applied to calculate the location of the epileptic source within the solution space based on the voltage map of that precise time point. The high temporal resolution provided by this tool is considered key for visualization of spreading of epileptiform activity.

The forward model can be based on a normalized head or, more precisely, on the individual MRI (**Figure 1d**). In any case, both must previously undergo cortical grey matter segmentation (**Figure 1e**) in order to define the solution space (**Figure 1f**, areas within the brain where the epileptic source will be allowed to be located). We will discuss the benefits of applying single subject MRI together with ESI, as well as the technical limitations encountered, in the following section.

### Methodological considerations of ESI

Conversely to single waveform analysis of EEG, ESI is based on spatial analysis of the potential maps; therefore, the quality of these maps will set the ground for further analysis. In this sense, it is vital that these scalp potential fields are properly acquired and analysed. Suitable recording of the potential field of the scalp, in terms of electrode number (spatial sampling) and positioning, is necessary in order to proceed with the analysis of the collected data. During the pre-processing period, artefact detection and suppression is crucial, in order to obtain a good signal-to-noise ratio. Once the data has been processed, source reconstruction can be carried out in a template brain of the Montreal Neurological Institute (MNI) or, more accurately, in the individual MRI.



**Figure 1: Principle of EEG Source Imaging**

Source localization methods rely on mathematical models of the bio-electrical generators and the volume conductors within which they lie. On the one hand, the inverse problem relies in identifying the intracranial generators from the measured potentials (b, c) recorded from a large array of electrodes (a). On the other hand, the forward problem consists in modeling the scalp electromagnetic fields produced by a known source configuration. These models are based on the segmentation of the individual MRI and the grey matter (d, e). A regular grid of solution points in the gray matter is determined and the lead field matrix is computed using the known analytical solutions for a head model (f).

### a) Spatial sampling

The optimum number of electrodes required for adequately sampling the potential field has been debated. Standard clinical EEG proposes a setup of some few electrodes (around 20) with a relatively large inter-electrode distance (around 6 cm). In the early 90s, several studies were carried out claiming that 3 cm is the minimum inter-electrode distance necessary for proper sampling of the underlying brain sources [26-28]. These findings were validated by a study in a group of 14 patients with refractory focal epilepsy which showed that source localization precision to a sub-lobar level is possible when using an electrode setup of more than 63 electrodes [16, 29]. Further increase from 64 to 128 channels showed less significant improvement.

Recent research took into account the different conduction properties and resistivity that exist between skull and brain, and claimed that the brain/skull con-

ductivity ratio is higher than previously estimated [30-34]; therefore, a larger number of electrodes would help to solve this issue. In addition, different conduction properties between the pediatric population and adults have been described [35, 36]. These new studies concluded that even more than 100 channels would be required to optimally sample the brain electric fields. A more recent study was performed using a more restrictive head model (finite difference model) and realistic values for brain/skull conductive characteristics; showing that improvement in terms of localization can be attained with up to 256 scalp electrodes [37].

### b) Electrode position

Electrode position is an additional factor that should be taken into account while interpreting the potential field. In principle, the electrode array should cover the

entire scalp surface rather than a circumscribed sector, in order to attain a complete electric field showing all positive and negative potentials. For instance, since conventional 10/20 EEG system does not incorporate inferior electrodes, medio-temporal sources are often misplaced [38]. In case that only low resolution EEG is available, a complete coverage of the scalp should be ensured.

### c) Artifact detection and elimination

While applying multiple electrodes covering the scalp surface, the risk of having bad contacts during the recording cannot be avoided. Once the data was collected, offline detection by either suppressing or “interpolating” bad electrodes from the neighboring electrodes using a spline interpolation algorithm can be performed [39]. In case an artifact is observed in multiple electrodes at the same time point, methods such as independent component analysis (ICA) can be applied. This method relies on the hypothesis that brain activity is the result of a superimposition of several independent activities [40].

### d) Individual vs. Template MRI

Up to now, most choices have been reduced to the following question: do we intend to carry out an analysis on an individual or a group basis? On the one hand, selection of a template brain provides a direct interface between the subject’s source and template space, permitting all sorts of group analysis [41]. Nevertheless, this would not be valid in patients having large brain abnormalities altering the skull/brain conductivity, in which an individual-based analysis would be required (**Figure 2**). On the other hand, a recent study revealed significant differences while comparing the localization yield of high-resolution source imaging while using individual MRI versus MNI [42]. This would mean that, from a surgical point of view, the epileptogenic zone will be more precisely delimited using individual MRI and that, in addition, further post-operative risks could be reduced.

### ESI: estimating the epileptic focus

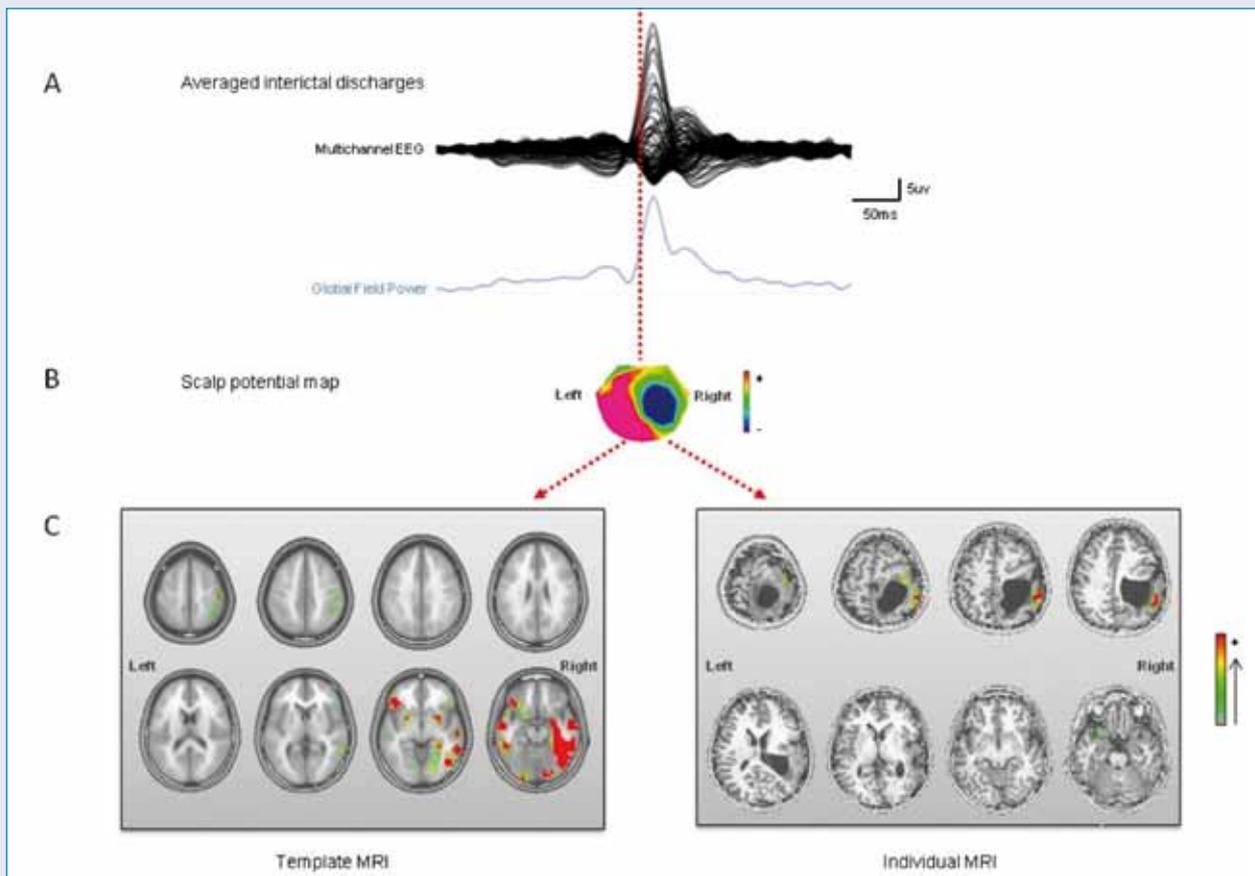
The clinical field in which EEG mapping has been used the most is probably in presurgical evaluation of patients presenting with medically intractable epilepsy. ESI, in combination with advanced inverse solution methods, has shown successful results even in epileptic patients with diverse clinical features (i.e. age, lesion size, localization).

ESI has already proven its worth in patients with lesional epilepsy. As shown in previous studies, this tech-

nique is capable to localize brain sources arising from extra-temporal up to deep mesio- and latero-temporal localizations [43, 44]. A study carried out in 30 post-operatively seizure-free paediatric patients of whom 13 had temporal lobe epilepsy, using 29 electrodes and the patient’s individual MRI, reported a correct localization of 90% at a lobar level [38]. Conversely, the same success rate was not observed when including only temporal lobe epilepsy patients, due to an insufficient electrode coverage of the basal temporal areas (i.e. low resolution ESI) [45]. For temporal epilepsy, increased spatial sampling allowed successful localisation in those cases that showed discordant results with ESI performed on clinical recordings (for more details see “Methodological considerations of ESI”). More precisely, in a series of 152 epileptic patients, ESI based on high-resolution EEG (>64 electrodes) and individual MRI as a head model rendered the highest sensitivity of 84% (defined as % of seizure free patients with focus localization within the resected zone) and specificity of 88% (defined as % of patients with focus localization outside the operated area) as compared to standard EEG recordings (19-29 electrodes) which showed a sensitivity of 66% [42].

From a hypothetical perspective, because EEG is affected by conductivity changes, the use of ESI was felt to be limited when studying patients with large brain lesions. Previous simulation studies have addressed this question, but were incapable to answer whether in case of individual’s data, accuracy of ESI is still satisfactory [46, 47]. A recent study showed that ESI is able to properly localize the epileptogenic zone in 12/14 patients with very large brain lesions (**Figure 2**) notwithstanding the conductivity changes [48]. Conversely to prior research, this group used a more precise head model and a reconstruction based on spherical deformation of the individual grey matter known as “SMAC” [23]. The same authors discussed the application of ESI in patients with no apparent brain lesion; being capable of appropriately localizing the epileptic focus in 8/10 cases [13]. The interest of this research lies on the fact that previous studies of postsurgical outcome in this group of patients showed that around half of them would not become seizure-free in spite of an exhaustive pre-surgical evaluation [49, 50]. In this regard, ESI would provide relevant information, concerning the epileptogenic focus in this particularly difficult group of patients in which MRI provides no significant information.

Despite these interesting findings, one concern regarding ESI for pre-surgical epilepsy evaluation is that the analysis solely relies on interictal changes rather than ictal activity. While interictal activity might provide beneficial information, it does not always seem to correspond with the seizure onset area [51, 52]. On the other hand, ictal EEG patterns are essential for determining the origin and spread of epileptic activity [53]. However, its application has been hampered due



**Figure 2: EEG Source Imaging for the localization of interictal epileptiform discharges in patients with large brain lesions** (A) Averaged interictal discharges recorded from 128 channel-EEG, displayed on a butterfly plot (overlaid traces) and referenced to the average reference. Global field power (GFP) curve is depicted in blue. The time point corresponding to the 50% rising phase of the average interictal discharge is plotted in a red-dotted line. (B) Scalp potential map corresponding to the aforementioned time point (red, positive voltage; blue, negative voltage). (C) Source localization with a linear distributed inverse solution in the template MRI (left) and the individual MRI (right) at a single time point of GFP peak. Maximal activity is seen on the right parietal lobe while using the individual MRI, whereas template MRI depicts a more distributed activation and maximal in the right temporal lobe, with activity even within the LCR-filled cavity.

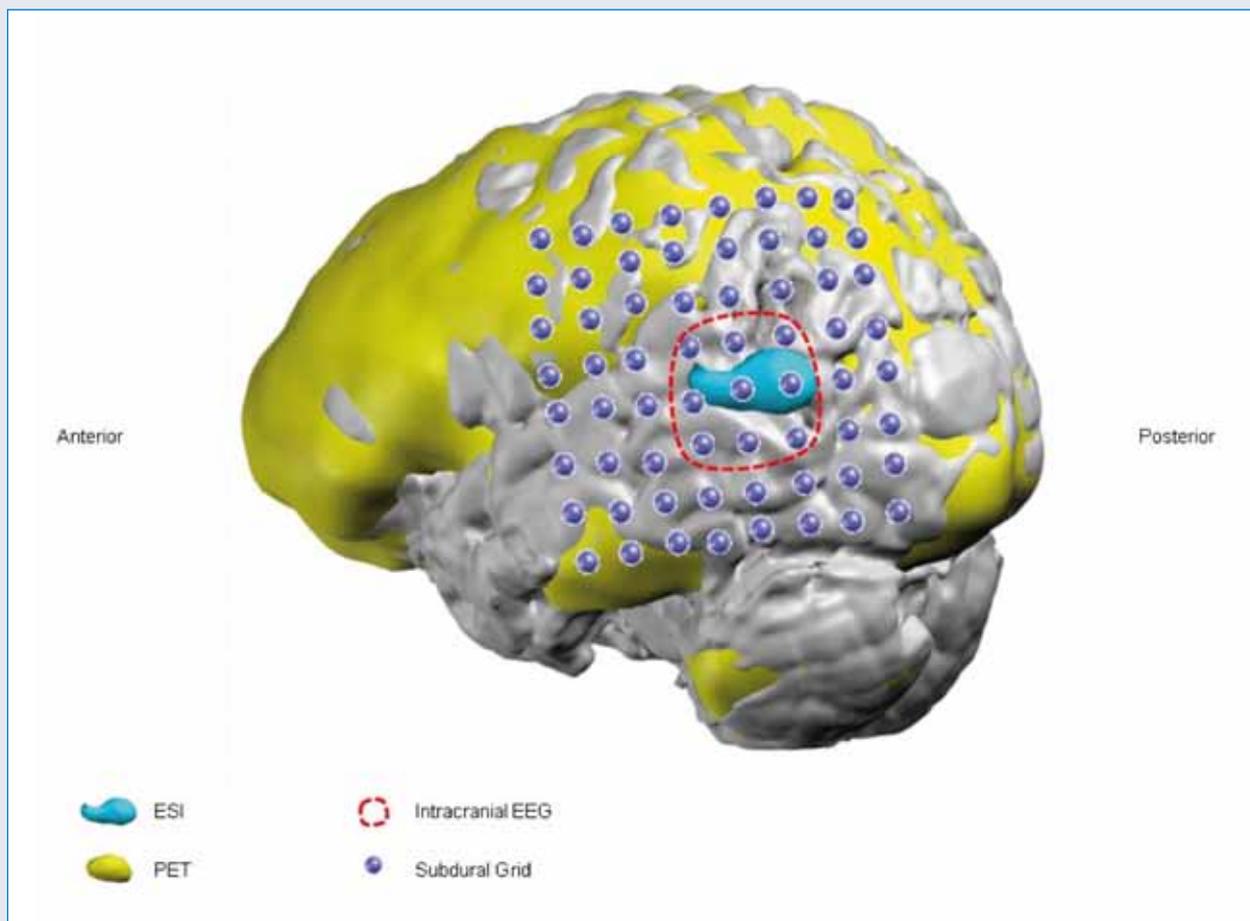
to the large amount of artefact and the low signal-to-noise ratio. A number of ictal long-term monitoring (LTM) studies in adults have shown promising results that were concordant with clinical presentation and intracranial EEG recordings [54, 55]. Since high-resolution EEG long-term systems are available, the use of ESI in spike analysis is now possible and could be of great interest since it is thought to reflect the epileptogenic area. In the following segment we will discuss the advent of LTM recordings and spike analysis in the framework of presurgical epilepsy evaluation.

### Long term monitoring (LTM) and ESI of ictal epileptiform activity

Since the early 80s, in-patient LTM recording of video-EEG is routinely applied in preoperative assessment of epilepsy using few numbers of electrodes (i.e. less than 30) [56]. Nowadays, recent software development

allows dense array (up to 256 electrodes) video-EEG LTM to be recorded for numerous days. Since recordings are carried out during various hours (>24), LTM can easily capture multiple seizures, as opposed to other non-invasive techniques (i.e. SPECT, MEG). The main aim is to determine the lateralization or estimated localization of the seizure onset area. Nonetheless, in order to assess its worthiness, direct comparison with more well established techniques is needed.

In a LTM study using high resolution ESI (up to 256 channels), the surface ictal patterns of 10 medically intractable epileptic patients were compared to gold standard sEEG, and a high level of agreement between both techniques was obtained [55]. However, this study supplies restricted information (i.e. source localization) coming from only the selected spike at seizure onset, disregarding the temporal and spatial propagation of ictal activity. Rare scalp EEG studies have been focused in improving the analysis of seizure activity by applying diverse approaches ranging from full scalp frequency



**Figure 3: Multimodal imaging in a presurgical evaluation workup.**

A 15-year-old female patient diagnosis with a tuberous sclerosis and a drug-resistant epilepsy who underwent interictal PET coregistered with the MRI (depicted in yellow) and ESI of interictal epileptiform discharges (depicted in pale blue) prior to intracranial electrode implantation. A large hypometabolism is seen concordant with the ESI maximum. Subsequently, the patient underwent subdural grid implantation which was also co-registered with the MRI. Intracranial EEG analysis showed a restricted area of ictal onset (illustrated with a red-dotted square). The ESI result of the patient shows a perfect correspondence with the subdural electrode recordings.

analysis described in terms of source space [57] or temporal evolution [58], to space-oriented temporal segmentation (i.e. functional microstates) on multichannel EEG data [12] in combination with different source-imaging algorithms. In a recent study, 8 drug-resistant epileptic patients were recorded with a LTM 76-channel EEG system and seizure onset zone was properly identified in 6/8 (2 cases presented false positive results) cases by means of independent component analysis [59].

The aforementioned studies aimed at localizing the seizure onset zone. On the other hand, other research groups have been trying to determine the so-called pre-ictal state (i.e. few minutes prior to seizure onset) by means of automated seizure detection algorithms (for a review see [60]). This would provide a new perspective into understanding the mechanisms of seizure generation. However, to our knowledge, no research has intended to characterize the underlying changes during pre-ictal period. Pattern recognition methods have been applied to investigate brief functional EEG

changes by determining a series of periods of stable map configuration (brain functional “microstates”) [61]; and 4 stable microstates were characterized in the spontaneous EEG of awake healthy adults [62-64]. It can be hypothesized that abnormal microstates patterns can be found a few minutes prior to seizure onset. In a multicentric scientific project (SNF 33CM30-124089, SPUM epilepsy), we are currently investigating the temporal and spatial properties of large-scale epileptic network. We apply multichannel (>64 electrodes) analysis of the resting EEG in the time domain, in a large population of extra-temporal and temporal lobe epilepsy patients to describe the behavior of the different microstate classes during the pre-ictal state.

## Comparison with other non-invasive techniques

In addition to LTM EEG recording, presurgical workup includes the following techniques: high-resolution MRI, PET and SPECT. Nevertheless, when these methods are unable to precisely localize the epileptogenic focus, invasive recordings from surgically implanted electrodes might be required [65]. In these cases, accurate localization of the seizure zone with a priori hypothesis allows better preparation for intracranial electrode implantation.

From a clinical point of view, ESI is a very alluring non-invasive technique which provides a superior temporal resolution (Figure 3), in the millisecond range, as compared to those methods based on changes in metabolic or vascular correlates of neural activity [66, 67]. From a practical perspective, this type of examination does not require sedation, it can be performed at patient's bedside and it is, therefore, suitable in the pediatric population and cognitively impaired patients.

The abovementioned prospective study of Brodbeck et al. compared the results of ESI (low or high-resolution analyzed using either individual MRI or template head model) with other well defined imaging tools such as MRI, PET and SPECT in a group of 152 operated epileptic patients with a follow-up period of more than 1 year [42]. A total of 43 patients underwent all examinations; showing that high-resolution ESI using individual MRI rendered the highest sensitivity (80%) and, principally, specificity rate (88%), followed by MRI (71.4% and 50%), PET (62.9% and 37.5%) and SPECT (54.3% but a higher specificity as compared to MRI and PET of 62.5%).

## Conclusion

ESI is a reliable non-invasive imaging tool that, due to technical progress, can be easily applied in a clinical setup and does not require highly experienced personnel. Commercially available EEG recordings allow short and comfortable sessions and, even, long-term monitoring acquisitions are possible. In addition, recent research has demonstrated the advantage of ESI, in terms of localization precision, over other non-invasive functional methods in a large prospective study.

## References

1. Sander JW. The epidemiology of epilepsy revisited. *Curr Opin Neurol* 2003; 16: 165-170
2. Picot MC, Baldy-Moulinier M, Daurès JP et al. The prevalence of epilepsy and pharmaco-resistant epilepsy in adults: a population-based study in a Western European country. *Epilepsia* 2008; 49: 1230-1238
3. Luoni C, Bisulli F, Canevini MP et al. Determinants of health-related quality of life in pharmaco-resistant epilepsy: results from a large multicenter study of consecutively enrolled patients using validated quantitative assessments. *Epilepsia* 2011; 52: 2181-2191

4. Engel J, Jr. Clinical neurophysiology, neuroimaging, and the surgical treatment of epilepsy. *Curr Opin Neurol Neurosurg* 1993; 6: 240-249
5. Kassubek J, Sperfeld AD, Baumgartner A et al. Brain atrophy in pure and complicated hereditary spastic paraparesis: a quantitative 3D MRI study. *Eur J Neurol* 2006; 13: 880-886
6. Knowlton RC, Elgavish RA, Bartolucci A et al. Functional imaging: II. Prediction of epilepsy surgery outcome. *Ann Neurol* 2008; 64: 35-41
7. Henry TR, Van Heertum RL. Positron emission tomography and single photon emission computed tomography in epilepsy care. *Semin Nucl Med* 2003; 33: 88-104
8. Binnie CD, Stefan H. Modern electroencephalography: its role in epilepsy management. *Clin Neurophysiol* 1999; 110: 1671-1697
9. Abraham K, Marsan CA. Patterns of cortical discharges and their relation to routine scalp electroencephalography. *Electroencephalogr Clin Neurophysiol* 1958; 10: 447-461
10. Hamer HM, Morris HH, Mascha EJ et al. Complications of invasive video-EEG monitoring with subdural grid electrodes. *Neurology* 2002; 58: 97-103
11. Seeck M, Spinelli L. Intracranial monitoring. *Suppl Clin Neurophysiol* 2004; 57: 485-493
12. Lantz G, Michel CM, Seeck M et al. Space-oriented segmentation and 3-dimensional source reconstruction of ictal EEG patterns. *Clin Neurophysiol* 2001; 112: 688-697
13. Brodbeck V, Spinelli L, Lascano AM et al. Electrical source imaging for presurgical focus localization in epilepsy patients with normal MRI. *Epilepsia* 2010; 51: 583-591
14. Michel CM, Grave de Peralta R, Lantz G et al. Spatiotemporal EEG analysis and distributed source estimation in presurgical epilepsy evaluation. *J Clin Neurophysiol* 1999; 16: 239-266
15. Ray A, Tao JX, Hawes-Ebersole SM, Ebersole JS. Localizing value of scalp EEG spikes: a simultaneous scalp and intracranial study. *Clin Neurophysiol* 2007; 118: 69-79
16. Lantz G, Spinelli L, Seeck M et al. Propagation of interictal epileptiform activity can lead to erroneous source localizations: a 128-channel EEG mapping study. *J Clin Neurophysiol* 2003; 20: 311-319
17. Lehmann D. Spatial analysis of EEG and evoked potential data. In: Duffy FH (ed): *Topographic Mapping of Brain Electrical Activity*. Massachusetts: Butterworth, 1986: 29-61
18. Srebro R, Oguz RM, Hughlett K, Purdy PD. Functional brain imaging: dipole localization and Laplacian methods. *Vision Res* 1993; 33: 2413-2419
19. Fender DH. Models of the human brain and the surrounding media: their influence on the reliability of source localization. *J Clin Neurophysiol* 1991; 8: 381-390
20. Vieth J. [Localization accuracy of biomagnetic signals]. *Fortschr Med* 1991; 109: 683-684
21. Scherg M, Von Cramon D. Evoked dipole source potentials of the human auditory cortex. *Electroencephalogr Clin Neurophysiol* 1986; 65: 344-360
22. Michel CM, Murray MM, Lantz G et al. EEG source imaging. *Clin Neurophysiol* 2004; 115: 2195-2222
23. Spinelli L, Andino SG, Lantz G et al. Electromagnetic inverse solutions in anatomically constrained spherical head models. *Brain Topogr* 2000; 13: 115-125
24. Bertrand O, Thévenet M, Perrin F. 3D finite element method in brain electrical activity studies. In: Nenonen HMRJ, Katila T (eds): *Biomagnetic Localization and 3D Modeling*. Helsinki: Helsinki University of Technology, 1991: 154-171

25. Meijs JW, Bosch FG, Peters MJ, Lopes da Silva FH. On the magnetic field distribution generated by a dipolar current source situated in a realistically shaped compartment model of the head. *Electroencephalogr Clin Neurophysiol* 1987; 66: 286-298
26. Gevins A, Brickett P, Costales B et al. Beyond topographic mapping: towards functional-anatomical imaging with 124-channel EEGs and 3-D MRIs. *Brain Topogr* 1990; 3: 53-64
27. Spitzer AR, Cohen LG, Fabrikant J, Hallett M. A method for determining optimal interelectrode spacing for cerebral topographic mapping. *Electroencephalogr Clin Neurophysiol* 1989; 72: 355-361
28. Srinivasan R, Tucker D, Murias M. Estimating the spatial Nyquist of the human EEG. *Behavior Research Methods Instruments & Computers* 1998; 30: 8-19
29. Lantz G, Grave de Peralta R, Spinelli L et al. Epileptic source localization with high density EEG: how many electrodes are needed? *Clin Neurophysiol* 2003; 114: 63-69
30. Gonçalves S, de Munck JC, Verbunt JP et al. In vivo measurement of the brain and skull resistivities using an EIT-based method and the combined analysis of SEF/SEP data. *IEEE Trans Biomed Eng* 2003; 50: 1124-1128
31. Gonçalves SI, de Munck JC, Verbunt JP et al. In vivo measurement of the brain and skull resistivities using an EIT-based method and realistic models for the head. *IEEE Trans Biomed Eng* 2003; 50: 754-767
32. Lai Y, van Drongelen W, Ding L et al. Estimation of in vivo human brain-to-skull conductivity ratio from simultaneous extra- and intra-cranial electrical potential recordings. *Clin Neurophysiol* 2005; 116: 456-465
33. Ryyänänen O, Hyttinen J, Malmivuo J. Study on the spatial resolution of EEG – effect of electrode density and measurement noise. *Conference Proceedings – IEEE Eng Med Biol Soc* 2004; 6: 4409-4412
34. Ryyänänen OR, Hyttinen JA, Malmivuo JA. Effect of measurement noise and electrode density on the spatial resolution of cortical potential distribution with different resistivity values for the skull. *IEEE Trans Biomed Eng* 2006; 53: 1851-1858
35. Fifer WP, Grieve PG, Grose-Fifer J et al. High-density electroencephalogram monitoring in the neonate. *Clinics in Perinatology* 2006; 33: 679-691
36. Grieve PG, Emerson RG, Isler JR, Stark RI. Quantitative analysis of spatial sampling error in the infant and adult electroencephalogram. *Neuroimage* 2004; 21: 1260-1274
37. Lantz G, Brodbeck V, Seeck M et al. Electric source imaging – Increasing the number of electrodes to 256 improves source localization precision of interictal epileptiform activity. *Epilepsia* 2009; 50(Suppl 11): 163
38. Sperli F, Spinelli L, Seeck M et al. EEG source imaging in pediatric epilepsy surgery: a new perspective in presurgical workup. *Epilepsia* 2006; 47: 981-990
39. Perrin F, Pernier J, Bertrand O et al. Mapping of scalp potentials by surface spline interpolation. *Electroencephalogr Clin Neurophysiol* 1987; 66: 75-81
40. Hyvarinen A, Oja E. Independent component analysis: algorithms and applications. *Neural Netw* 2000; 13: 411-430
41. Litvak V, Friston K. Electromagnetic source reconstruction for group studies. *Neuroimage* 2008; 42: 1490-1498
42. Brodbeck V, Spinelli L, Lascano AM et al. Electroencephalographic source imaging: a prospective study of 152 operated epileptic patients. *Brain* 2011; 134: 2887-2897
43. Lantz G, Ryding E, Rosen I. Dipole reconstruction as a method for identifying patients with mesolimbic epilepsy. *Seizure* 1997; 6: 303-310
44. Zumsteg D, Friedman A, Wennberg RA, Wieser HG. Source localization of mesial temporal interictal epileptiform discharges: correlation with intracranial foramen ovale electrode recordings. *Clin Neurophysiol* 2005; 116: 2810-2818
45. Michel CM, Lantz G, Spinelli L et al. 128-channel EEG source imaging in epilepsy: clinical yield and localization precision. *J Clin Neurophysiol* 2004; 21: 71-83
46. Benar CG, Gotman J. Modeling of post-surgical brain and skull defects in the EEG inverse problem with the boundary element method. *Clin Neurophysiol* 2002; 113: 48-56
47. Vatta F, Bruno P, Inchingolo P. Improving lesion conductivity estimate by means of EEG source localization sensitivity to model parameter. *J Clin Neurophysiol* 2002; 19: 1-15
48. Brodbeck V, Lascano AM, Spinelli L et al. Accuracy of EEG source imaging of epileptic spikes in patients with large brain lesions. *Clin Neurophysiol* 2009; 120: 679-685
49. Blume WT, Ganapathy GR, Munoz D, Lee DH. Indices of resective surgery effectiveness for intractable nonlesional focal epilepsy. *Epilepsia* 2004; 45: 46-53
50. Jayakar P, Dunoyer C, Dean P et al. Epilepsy surgery in patients with normal or nonfocal MRI scans: integrative strategies offer long-term seizure relief. *Epilepsia* 2008; 49: 758-764
51. Alarcon G, Guy CN, Binnie CD et al. Intracerebral propagation of interictal activity in partial epilepsy: implications for source localisation. *J Neurol Neurosurg Psychiatry* 1994; 57: 435-449
52. So N, Gloor P, Quesney LF et al. Depth electrode investigations in patients with bitemporal epileptiform abnormalities. *Ann Neurol* 1989; 25: 423-431
53. Ebersole JS, Pacia SV. Localization of temporal lobe foci by ictal EEG patterns. *Epilepsia* 1996; 37: 386-399
54. Koessler L, Benar C, Maillard L et al. Source localization of ictal epileptic activity investigated by high resolution EEG and validated by SEEG. *Neuroimage* 2010; 51: 642-653
55. Holmes MD, Tucker DM, Quiring JM et al. Comparing noninvasive dense array and intracranial electroencephalography for localization of seizures. *Neurosurgery* 2010; 66: 354-362
56. Binnie CD, Rowan AJ, Overweg J et al. Telemetric EEG and video monitoring in epilepsy. *Neurology* 1981; 31: 298-303
57. Lantz G, Michel CM, Seeck M et al. Frequency domain EEG source localization of ictal epileptiform activity in patients with partial complex epilepsy of temporal lobe origin. *Clin Neurophysiol* 1999; 110: 176-184
58. Blanke O, Lantz G, Seeck M et al. Temporal and spatial determination of EEG-seizure onset in the frequency domain. *Clin Neurophysiol* 2000; 111: 763-772
59. Yang L, Wilke C, Brinkmann B et al. Dynamic imaging of ictal rhythmic activity using dense-array EEG. *Conf Proc IEEE Eng Med Biol Soc* 2011; 2011: 8271-8274
60. Gotman J. Automatic detection of seizures and spikes. *J Clin Neurophysiol* 1999; 16: 130-140
61. Lehmann D, Ozaki H, Pal I. EEG alpha map series: brain micro-states by space-oriented adaptive segmentation. *Electroencephalogr Clin Neurophysiol* 1987; 67: 271-288
62. Van de Ville D, Britz J, Michel CM. EEG microstate sequences in healthy humans at rest reveal scale-free dynamics. *Proc Natl Acad Sci U S A* 2010; 107: 18179-18184
63. Britz J, Van De Ville D, Michel CM. BOLD correlates of EEG topography reveal rapid resting-state network dynamics. *Neuroimage* 2010; 52: 1162-1170
64. Strik WK, Lehmann D. Data-determined window size and space-oriented segmentation of spontaneous EEG map series. *Electroencephalogr Clin*

*Neurophysiol* 1993; 87: 169-174

65. Seeck M, Spinelli L. Intracranial monitoring. *Clin Neurophysiol* 2004; 57(Suppl): 481-489

66. Hari R, Karhu J, Hämäläinen M et al. Functional organization of the human first and second somatosensory cortices: a neuromagnetic study. *Eur J Neurosci* 1993; 5: 724-734

67. Tobimatsu S, Zhang YM, Kato M. Steady-state vibration somatosensory evoked potentials: physiological characteristics and tuning function. *Clin Neurophysiol* 1999; 110: 1953-1958

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### Summary

Simultaneous EEG/fMRI recordings offer a unique approach of characterizing epileptic brain activity. The combination of high temporal resolution of EEG recordings and high spatial resolution of fMRI add to enhance the localization of rapidly fluctuating epileptic sources in the brain parenchyma. Scalp EEG/fMRI is a non-invasive, safe and reproducible brain imaging technique and is increasingly implemented in the clinical pre-surgical workup of epilepsy surgery. Formal validation of the clinical value of EEG/fMRI recordings is challenging but current state of research suggests that EEG/fMRI analysis results in a comparable sensitivity compared to PET and SPECT imaging to identify the SOZ. In this review we discuss methodological considerations to identify and interpret epileptic activity in EEG/fMRI recordings, the proposed recent advances and ongoing challenges.

**Epileptologie 2012; 29: 90 – 98**

**Key words:** Epilepsy, EEG/fMRI, presurgical evaluation, hemodynamic response

### Neue Entwicklungen der simultanen EEG/fMRI in der Epilepsie – bereit für die klinische Anwendung?

Simultane EEG/fMRI-Ableitungen bieten eine einzigartige Möglichkeit, um epileptische Hirnaktivität zu charakterisieren. Die Kombination aus der hohen zeitlichen Auflösung der EEG-Aufnahme und die hohe räumliche Auflösung der fMRI hilft die schnell fluktuierenden epileptischen Quellen im Hirnparenchym zu lokalisieren. Skalp-EEG/fMRI ist eine nicht invasive, sichere und reproduzierbare Technik und wird zunehmend im Rahmen der prächirurgischen Abklärung eingesetzt. Die formale Validierung der EEG/fMRI-Untersuchung ist komplex, jedoch suggerieren die vorliegenden Studien, dass EEG/fMRI-Untersuchungen vergleichbar sensitiv sind wie PET- oder SPECT-Untersuchungen um die Anfallsursprungszone zu identifizieren. In diesem Review diskutieren wir methodologische

Überlegungen, wie epileptische Aktivität in der EEG/fMRI-Untersuchung identifiziert und interpretiert werden kann, in jüngerer Zeit entwickelte Lösungsvorschläge und die weiterhin offenen Fragen.

**Schlüsselwörter:** Epilepsie, EEG/fMRT, prächirurgische Diagnostik, hämodynamische Antwort

### Développements récents de l'électroencéphalographie et IRM fonctionnelle simultanées – un outil pour l'évaluation clinique ?

L'acquisition simultanée de l'électroencéphalogramme (EEG) et de l'IRM fonctionnelle (fMRI) offre une possibilité unique de caractériser l'activité épileptique cérébrale. La combinaison de l'EEG, possédant une résolution temporelle élevée, avec la fMRI, caractérisée par une haute résolution spatiale, permet d'obtenir au sein du parenchyme cérébral une localisation plus précise et dynamique de sources épileptiques rapidement fluctuantes. L'EEG/fMRI est une technique non-invasive, sûre et reproductible et tend à être de plus en plus utilisée lors de l'évaluation préchirurgicale des épilepsies pharmaco-résistantes. La validation formelle de l'EEG/fMRI est complexe, mais les données des études à disposition suggèrent que la sensibilité de l'EEG/fMRI pour identifier un foyer épileptique primaire est comparable à celle du PET ou du SPECT. Dans cette revue nous discutons de quelques aspects méthodologiques concernant l'identification et l'interprétation de l'activité épileptique au travers de l'enregistrement EEG/fMRI, des développements récemment proposés et des questions ouvertes à de futures recherches.

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<sup>2</sup> Crepeau AZ et al. Levetiracetam: a comprehensive review, Expert Rev Neurother, 2010 Feb, 10(2), 159–171

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**Mots clés :** Epilepsie, électroencéphalographie et IRM fonctionnelle simultanées, évaluation préchirurgicale, réponse hémodynamique

## 1. Introduction

The development of electroencephalogram (EEG) recordings simultaneous to functional MRI (fMRI) in the late 1990 was clinically motivated by the limited power of EEG to localize electrical sources of neuronal activity, in particular in deep brain structures [1]. In epilepsy, EEG/fMRI provides a unique opportunity to investigate simultaneously the fluctuations of the EEG signal representing synaptic activity of cortical pyramidal neurons and the hemodynamic responses (HR) of the blood oxygen level-dependent (BOLD) signal [2]. The combination of high temporal resolution of EEG recordings and high spatial resolution of fMRI add to enhance the localization of rapidly fluctuating epileptic sources in the brain parenchyma. EEG/fMRI has proven to be a noninvasive, safe and reproducible brain imaging technique [3-5]. A framework of methodologic and clinical studies has transformed EEG/fMRI into a powerful tool to investigate the hemodynamic changes associated with spontaneous brain activity in epileptic networks. Currently, simultaneous EEG/fMRI recordings in clinical epileptology are carried out in Switzerland at the Inselspital Bern and Hôpitaux Universitaires de Genève. Both centers focus on the application of EEG/fMRI for presurgical evaluation in focal epilepsies and are working together in the consortium “Imaging large-scale networks in epilepsy” funded by the Swiss National Science Foundation (SNF). In the present review, we will focus on novel developments of simultaneous EEG/

fMRI. First, we review approaches to identify interictal epileptic activity on scalp EEG for later use in fMRI analysis. Second, strategies to interpret the HR to interictal epileptiform discharges (IEDs) are discussed. We review the literature and discuss the current clinical value of EEG/fMRI recordings in epilepsy and the potential of some recent methodological developments.

## 2. Methodological considerations and developments

Safety issues of MR imaging [6, 7] and technical details of acquisition and preprocessing of EEG/MRI have been reviewed previously [8, 9]. **Figure 1** recapitulates issues of EEG artifact generation inside the “hostile environment” of a MR scanner due to pulsed field gradients (EEG signal fluctuations due to time-varying MR imaging gradients) and human pulse activity (ballistocardiogram; EEG signal fluctuations time-locked to cardiac activity via the static magnetic field). It aims to demonstrate the technical challenge to obtain an EEG signal of sufficient quality to identify IEDs. Gradient and pulse artifacts can be removed using the template average artifact subtraction method (AAS) described previously by Allen [10, 3]. While higher field strengths of the MR scanner and gradient systems increase the sensitivity to detect HR to IEDs, they also increase the various types of artifacts on EEG recordings. Therefore, an increasing number of centers use novel approaches, as the recently described temporal independent component analysis (ICA), to identify residual artifacts especially the ballistocardiogram and eye-blinks [11, 12]. The basic idea of combined EEG/fMRI is to identify certain features in the EEG, which are subsequently used

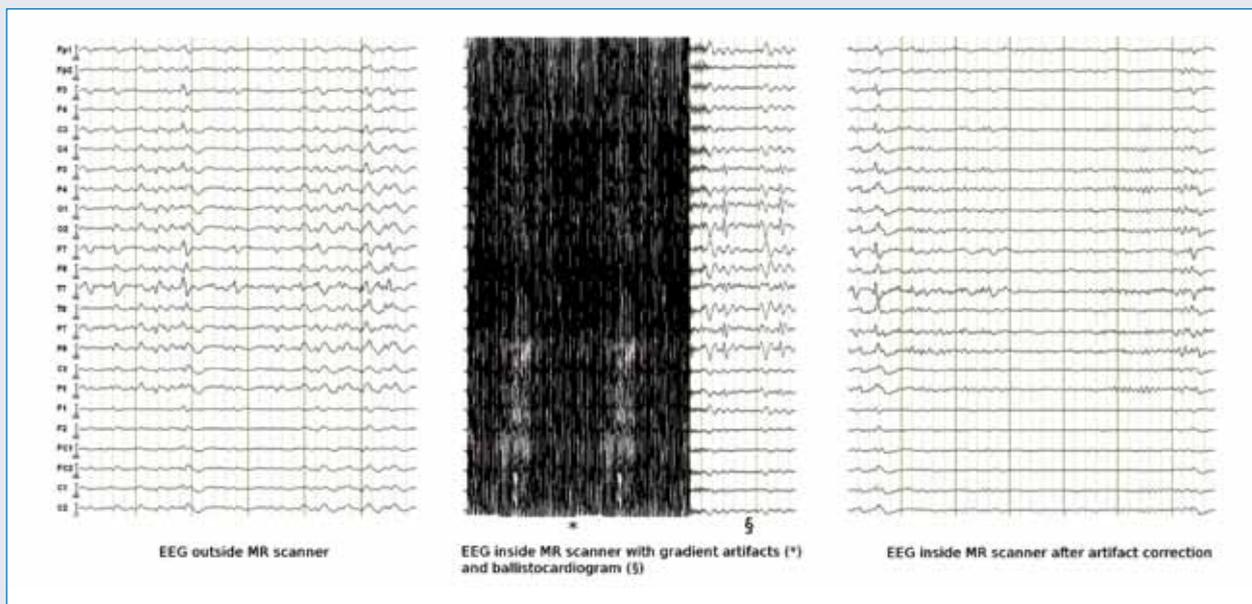


Figure 1

as predictors for the HR response. In epilepsy patients the most prominent feature is the presence of “spikes” on top of the background EEG. Therefore, the first and simplest approach to EEG/fMRI in epilepsy patients was to identify spikes visually, convolve the time series of spike timings with the hemodynamic response function (HRF) and subsequently analyze the spatial distribution of correlation of the BOLD signals with this predictor.

## 2.1 Interictal epileptic activity on surface EEG recordings

Prerequisite for the interpretation of EEG/fMRI is the detection of epileptic brain activity during the recording inside the MR scanner. The current strategies are based on visual or automated analysis of IEDs on the EEG recording after artifact removal [13, 14]. The temporal distribution of these IEDs are then processed as stereotyped “zero-duration” events in an event related model of the fMRI analysis (“spike-based” analysis). As the recording inside the MR scanner is confined to a restricted duration due to patient comfort and safety, there is a relevant portion of 40-70% of EEG/fMRI recordings without or with a limited number of IEDs. In these cases no significant HR can be detected [13, 15]. Importantly, only a fraction of interictal spikes recorded with intracranial electrodes can be identified on simultaneous scalp EEG recordings [16, 17]. Activity that is not detected on scalp EEG may, however, be associated with hemodynamic changes on BOLD fMRI [18]. This methodological issue results in challenges for EEG/fMRI recordings because time periods with interictal epileptic activity not fulfilling the criteria of spikes on visual scalp EEG may erroneously be attributed to the baseline signature of the fMRI signal. This introduces a bias towards false negative analysis results. In the following we discuss different approaches to overcome this limitation of EEG/fMRI recordings at least partly.

### a) ICA-based representation of IEDs

An alternative approach to extract IEDs in EEG/fMRI based on temporal ICA of surface EEG recordings has recently been developed by our group [19]. ICA is a computational method aiming at a separation of multivariate data into components (IC-factors, “sources”) that maximize the statistical independence. When following the ICA approach to IED identification, epileptic brain activity is a suitable representative of such an independent source. A limitation of this assumption is the increasingly recognized network aspect in genesis and propagation of epileptic activity and will be discussed below. In the ICA approach the IC-factor that codes epileptic activity best is manually selected on the basis of the temporal and spatial distribution of a set

of unequivocal IEDs. Contrary to single spike detection identification of IEDs based on IC-factors results in a continuous measure of the epileptic activity and thus provides more detailed and more objective information [20]. A principal advantage of the IC-based approach is the ability to model epileptic activity more physiologically, taking into account variation in amplitude, duration, and shape of IEDs, especially when high-resolution EEG is performed. Integration of individual amplitudes of IEDs in EEG/fMRI analysis has been recently reported to yield BOLD signal correlates that are more confined to the seizure onset zone (SOZ) [21, 19, 22, 23]. A good reliability of the IC-based approach has been reported to identify factors coding for the epileptic activity [24].

### b) Topographic based analysis

A novel approach proposed recently by Groullier et al. [25] is dedicated to EEG/fMRI recordings without visually detectable IEDs during EEG inside the scanner. In addition to the display of scalp EEG signals as a function of time, electrical activity can be represented by scalp voltage topographic maps (EEG maps). These topographic maps reflect the momentary activity of neuronal networks via the summation of post-synaptic cortical potentials over the whole brain. Changes in the activity of focal electrical brain generators influence the topography of these maps [26]. It has been shown that the topographic maps may reflect the electrical generators of focal epileptic activity [27]. These studies indicate that “the occurrence of these epilepsy-specific EEG maps in the resting EEG of individual patients represents an increase in the activity of the epileptic sources and could allow the detection of sub-threshold activity even in the absence of visually identifiable epileptic waveforms on the conventional EEG” [25]. The strength of the presence of these maps in the EEG recorded during functional MRI as a function of time was used as predictor for the hemodynamic changes in the epileptic network.

## 2.2. Hemodynamic changes linked to interictal epileptic activity

Most publications on EEG/fMRI were based on the assumption that IEDs are associated with a standard and predictable hemodynamic response and that hemodynamic changes occur time-locked to epileptic activity. The standard analysis model of fMRI assumes that following each spike or fluctuation of epileptic activity the BOLD signal changes according to a standard hemodynamic response function (HRF), defined and validated in brain activation studies in healthy subjects performing sensory or cognitive tasks [28]. Potential differences between patients, between different brain regions or between repeated individual recordings are

neglected, although HRF variability has been reported sizable [29]. In EEG/fMRI the majority of HR clearly diverging from the standard HRF were observed outside the SOZ in “distant BOLD correlates” and most likely represent effects of propagation [30]. As there is limited evidence of altered neurovascular coupling in the SOZ of epileptic brains, the use of the standard HRF with the delay of response maximum at approximately 6 s after the IED seems appropriate in most EEG/fMRI studies [28, 30, 31]. A second assumption in the analysis of HR is that the metabolic changes visualized on fMRI are representing exclusively epileptic neuronal activity. This might be not true.

### **2.2.1 HR at the SOZ**

The BOLD signal change linked to IEDs is variable, as indicated by various positive or negative BOLD correlates co-localizing to the SOZ in focal epilepsies [32, 13]. Explanations for this observation remain elusive. It is not clear whether the observed negative BOLD correlates reflect the effects of surround inhibition, impaired focal neurovascular coupling, large network influences resulting in a decreased metabolic rate or a vascular theft mechanism [32, 13]. Recently, it has been observed that BOLD changes can occur prior to the detection of interictal spikes detected on EEG [33]. These findings suggest that the metabolic (neuronal or glial) processes underlying spike-associated BOLD signal changes begin before electrical activity can be detected using scalp EEG [33, 34]. This observation has been further investigated by alternative modeling of the HR by temporally shifting the HRF function to the IEDs [35, 36] reporting pre-spike BOLD responses in the majority of investigated cases with focal epilepsy. The extent of BOLD correlates co-localizing with the SOZ in the pre-spike period is more focal and may be more specific than the HR to a simultaneous IEDs predictor or in the post-spike period. Hence, the analysis of HR occurring prior to IEDs on scalp spikes may, beyond potential pathophysiological insights be also of diagnostic relevance. Recent data from an animal study report absence of cortical epileptic activity in a region with HR preceding spikes suggesting an non-epileptic origin the observed hemodynamic phenomenon [37].

### **2.2.2 HR distant to the SOZ**

In the majority of simultaneous EEG/fMRI recordings in epilepsy HR are observed outside the area of the presumed SOZ, denominated „distant” or “remote” HR. The pathophysiology and clinical importance of such HRs have increasingly received attention in the past years. Both IEDs and seizures propagate (i.e. the pathological EEG patterns spread to distant areas) reflecting recruitment of neuronal activity in remote

brain areas [38, 39]. Although propagation of seizure activity may be well-defined, the propagation of epileptic activity occurring during seizure free periods is less well characterized. In focal epilepsies due to malformations of cortical development, distant BOLD correlates have been found in a variable distribution in cortical and subcortical structures [40]. Group analysis in homogeneous patient cohorts with temporal lobe epilepsies has reported a reproducible pattern of “distant” HR along structural pathways [41, 42]. The close overlay of the multi-focal pattern of HR and a cortical atrophy in mesio-temporal lobe epilepsy (MTLE) foster the hypothesis that the “distant” HR are not artifacts but rather represent a functionally and structurally characterized epileptic network involved in genesis and/or propagation of seizures (unpublished data). Distant BOLD correlates have also been characterized during the pre- and post-spike period in idiopathic generalized epilepsy (IGE), with spatial patterns typically resembling resting (or default) state networks of the brain (i.e. attention without specific activity) [43, 44]. Pathophysiological insights on the correlation between vigilance and epileptic activity, as it is clinically frequently observed, may disclose the understanding of large network influences on seizure generation. The spatial dispersion of whole brain HR in the pre- and post-spike period of two patients, suffering from IGE and focal epilepsy of temporal lobe origin, respectively, is further illustrated in two cases as follows:

#### **Illustrative case I**

A) 38 years old male with IGE presenting clinically generalized seizures, ictal and interictal generalized spike/wave pattern and no epileptogenic lesion on structural MRI. During simultaneous EEG/fMRI brief spike/wave discharges of a maximum duration of 3 s with bi-frontal dominance were recorded. Positive HR were found 10 s prior to the IEDs in the midline brainstem structures, evolving to a bilateral positive thalamic HR 8 s prior to the IEDs. Simultaneously to the IEDs and lasting for 10 s, a pattern of negative HR in the mesio-temporal, pontine and association cortices of the frontal, temporal and parietal lobe were delineated. The HR 10 s prior to IEDs in the brain stem corresponds potentially to hemodynamic alteration of the reticular system and may be involved in a modulation of vigilance known to precede IGE discharges. Following this reflection these HR would be of non-epileptic origin. The pattern of positive HR in the thalami and negative HR in the neocortex is considered typical for IGE. B) Scalp EEG recordings showing spike/wave discharges. C) Calculated IC-factor used for prediction of the HR.

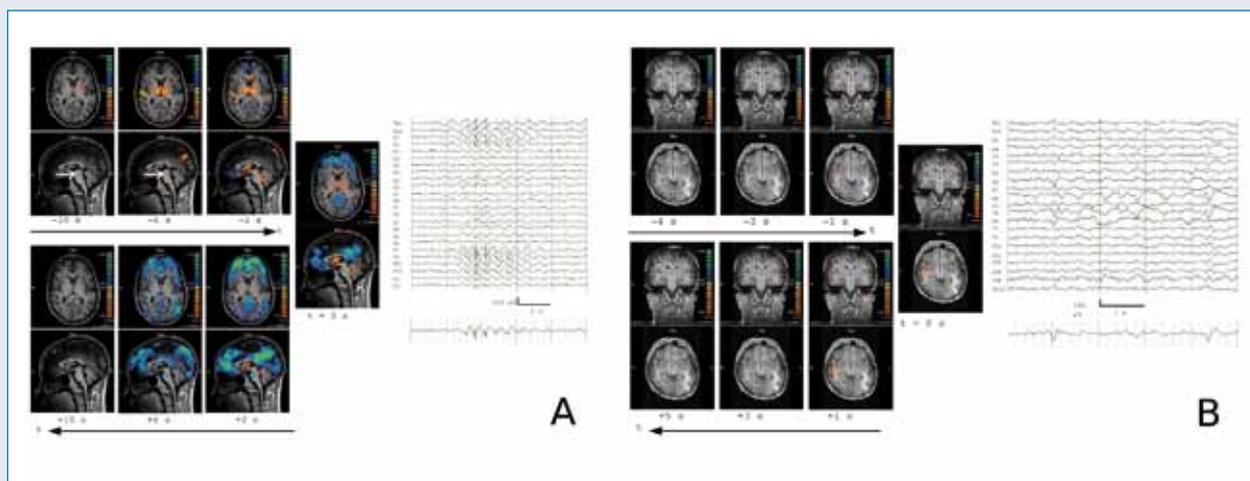


Figure 2: Illustrative Case I

### Illustrative case II

25 years old male with cryptogenic right temporal lobe epilepsy presenting an ictal semiology of acoustical hallucinations and secondary generalization, interictal right temporal spikes and no epileptogenic lesion on structural MRI. Here, already 4 s prior to isolated spikes temporal right on scalp EEG a focal positive HR in the lateral temporal lobe in the vicinity of Heschl's gyrus was present. The HR remained stable and focal for 9 s without clinical symptoms.

## 3. EEG/fMRI as clinical tool for presurgical epilepsy evaluation

### 3.1. Validation studies

Although combined EEG/fMRI studies have been conducted for 15 years up to now, evidence for clinical applications remains limited. Validation of EEG/fMRI as an alternative imaging technique is challenging as it has to be subjected to other available standards, ideally in large homogenous patient groups. Postoperative seizure freedom, in patients where the epileptogenic zone was successfully removed, represents the most clinically relevant form of validation. However, resected areas tend to extend beyond the epileptogenic zone and the SOZ, making it difficult to attribute the specificity of EEG/fMRI. Consequently, intracranial EEG recordings of seizures may be required to confirm inclusion of the SOZ. The limited spatial coverage of invasive EEG recordings is a potential drawback for method to method comparison. Recent studies have investigated the value of EEG/fMRI studies in the presurgical workup. One study aimed to attribute the potential role of EEG-fMRI

for clinical decision making in a cohort of patients who had previously been rejected for poorly localized epileptic focus or presumed multifocality [45]. About 14 percent of patients being initially no candidates for surgery were post hoc stratified for surgery. Another study that incorporated non-lesional frontal lobe epilepsies delineated the SOZ based on the results of simultaneous EEG/fMRI in 2 of 9 patients that subsequently underwent successful resection [46]. The co-localization of the most significant HR within the resected brain region (Peak activation, PA) has been repetitively related to good outcome in a limited number of patients [47, 15]. A recent study, reexamined the influence of the thresholding criterion used to determine HR to IEDs for the estimation of SOZ localization [48]. A newly introduced criterion based on a predefined extent of HR in the brain ("Fixed number of voxel", FAV) resulted in concordant localization of the SOZ to electroclinical data in 8 of 10 patients with good postsurgical outcome. Some limitations of established thresholding criteria as PA or the use of fixed thresholds (FWE) were renewed. (See Illustrative case III). Incorporation of scalp voltage topographic maps in patients without spikes during EEG/fMRI recordings resulted in the identification of HR in 78% of patients which were concordant to intracranial EEG/resected area [25]. Technical improvements of EEG/fMRI are nowadays targeted to incorporate EEG/fMRI in the workup of patients with MTLE by using the IC approach on the EEG [48, 19]. Most of the IEDs in the mesial temporal lobe have no correlate on visual scalp EEG and may thus erroneously be attributed to the baseline signature of the fMRI correlation. It could be demonstrated that epileptic activity extracted by an IC may partially overcome this limitation, thus making EEG/fMRI feasible in MTLE patients.

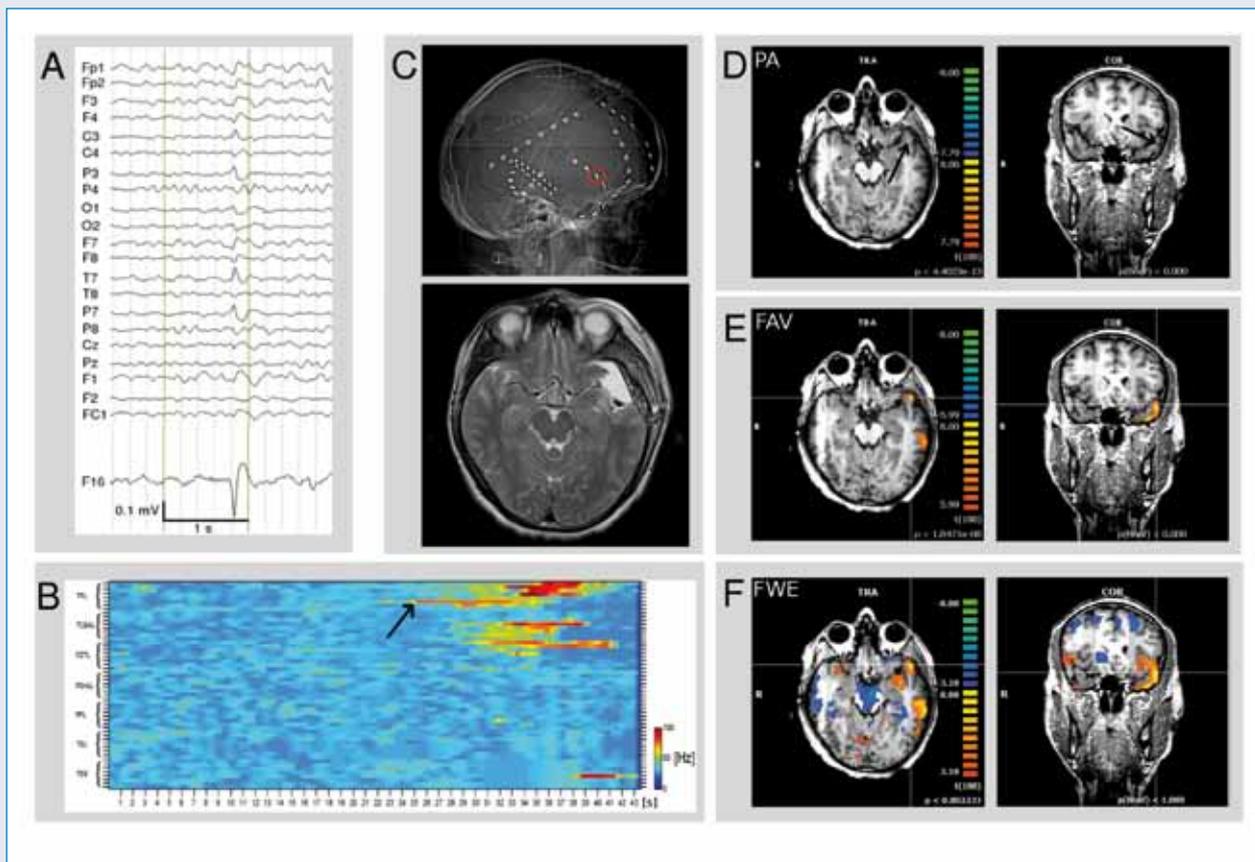


Figure 3: Illustrative Case II

### Illustrative case III

Patient with pharmaco-resistant non-lesional left lateral TLE. A - scalp EEG (average reference montage) and IC factor coding for the interictal spike with left temporal maximum. B - invasive EEG recording displaying high frequency oscillations on electrode TPL\_6 5 sec prior to clinical seizure onset and propagation on EEG. C - location of electrode TPL\_6 on the EEG implantation map (upper row) and postsurgical follow up MRI D (lower row) - Peak activation (PA) was located in the temporo-polar region (arrow). E - FAV criterion with temporo-lateral BOLD clusters in proximity to electrode TPL\_6. The distribution of BOLD clusters were used in the planning of the positioning of invasive EEG electrodes. F - FWE criterion discloses a widespread epileptic network.

### 3.2 Invasive EEG/fMRI

Simultaneous recordings of intracranial EEG and fMRI have been carried out recently following a strict safety protocol [49]. Even though the initial experiences seem encouraging and did not report any adverse effects, safety issues have to be further eluci-

dated. At least as long as the electrodes used for intracranial recordings lack approval for MRI by the manufacturers, the use of intracranial EEG/fMRI requires extremely careful ethical evaluation and the assessment of patients safety. Importantly, despite different waveforms and frequency characteristics, IEDs recorded from intracranial EEG can be modeled using a simple modeling approach similar to the one used for scalp EEG/fMRI. Intracranial EEG/fMRI demonstrated that BOLD signal changes matching the electrode contacts can be detected and hence key functional abnormalities of the epileptic brain can be monitored with this new technical approach [18].

### 3.3 EEG/fMRI during seizures

The vast majority of EEG/fMRI recordings are carried out in the interictal state. However, a large portion of diagnostic and therapeutic decisions are still based on ictal phenomena as seizure semiology or EEG patterns. Performing MRI during epileptic seizures has appreciable challenges and safety considerations. However, several EEG/fMRI studies in the ictal state have been made and were suitable for analysis [50-52, 14, 53]. Hyper-perfusion of the SOZ during seizures is established

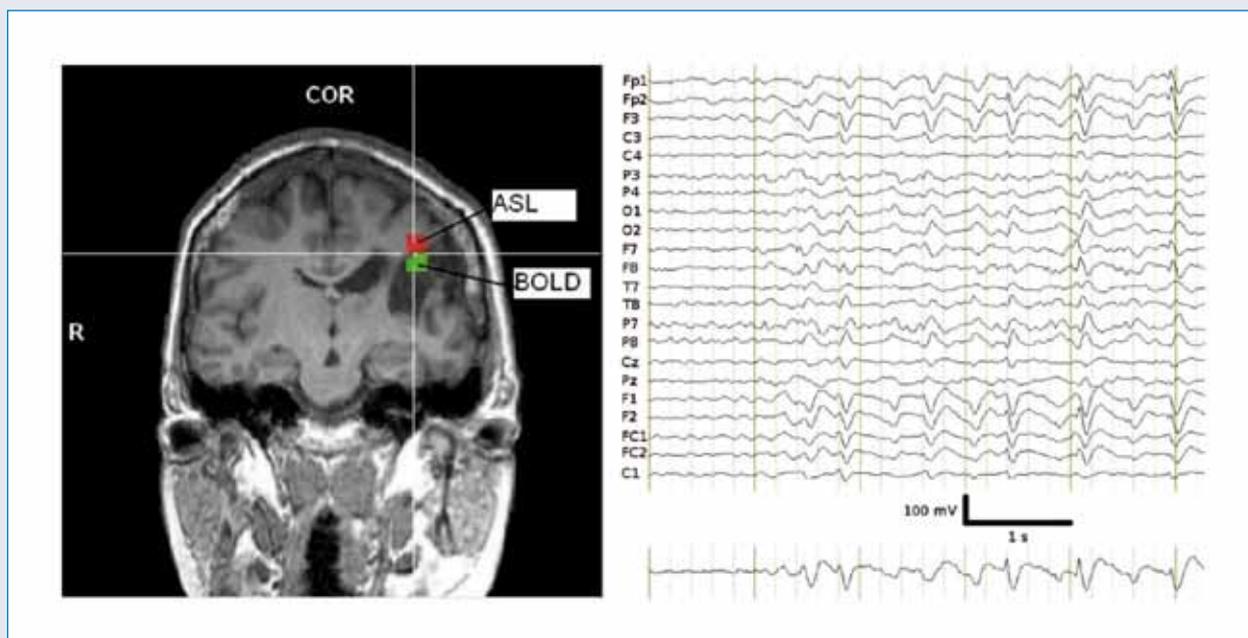


Figure 4: Illustrative Case III

since Penfield's experiments in 1933 and was consistently detected during ictal brain perfusion studies [54, 55]. Ictal EEG/fMRI recordings consistently show positive BOLD correlates encompassing the presumed SOZ. The intensity of the ictal neuronal and metabolic processes frequently result in widespread HR patterns, occasionally limiting the interpretability of EEG/fMRI recordings [56]. Illustrative case IV shows the tight spatial relation between the positive BOLD correlates adjacent to a chronic vascular epileptogenic lesion and the associated ictal hyper-perfusion. To date there is no evidence that the localization of HR in ictal EEG/fMRI recordings is more reliable in respect to the SOZ identification than in interictal recordings.

#### Illustrative case IV

Ictal EEG/fMRI during simple motor seizures - Left side: Structural T1 weighted MRI with chronic ischemic lesion in the territory of the left middle cerebral artery. Overlay of the maximum HR to epileptic EEG activity during simple motor seizures (BOLD in green) and the maximum of focal cerebral blood flow as measured by arterial spin labeling during an consecutive seizure (ASL in red). Right side: scalp EEG (average reference montage) and IC factor coding for the ictal epileptic activity with left frontal predominance during twitches of the right arm.

#### 4. Summary

Simultaneous EEG/fMRI recordings offer a unique approach of characterizing epileptic brain activity. Scalp EEG/fMRI is a non-invasive, safe and reproducible brain imaging technique. The underlying processes giving rise to epileptic EEG signal fluctuations and the associated hemodynamic changes on BOLD fMRI may not be completely identical and make interpretation of the EEG/fMRI results complex. The current state of research suggests that EEG/fMRI analysis results in a comparable sensitivity compared to PET and SPECT imaging [57, 58] to identify the SOZ. It may consequently be implemented as a complementary tool for presurgical evaluation of epilepsy patients. In addition, in the individual patient simultaneous EEG/fMRI may support the planning of intracranial EEG electrodes. Adding converging evidence to a clinical and EEG-derived hypothesis by non-invasive EEG/fMRI, may elude techniques that carry radiation exposure or, in selected cases, invasive EEG. From a scientific perspective, the technique provides a powerful opportunity to study functional changes in the entire epileptic brain aiming towards better understanding of the precise spatio-temporal pathophysiological mechanisms of epilepsy.

#### References

1. Ives JR, Warach S, Schmitt F et al. Monitoring the patient's EEG during echo planar MRI. *Electroencephalogr Clin Neurophysiol* 1993; 87: 417-420
2. Ogawa S, Lee TM, Kay AR, Tank DW. Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proc Natl Acad Sci U S A*

- 1990; 87: 9868-9872
3. Allen PJ, Polizzi G, Krakow K et al. Identification of EEG events in the MR scanner: the problem of pulse artifact and a method for its subtraction. *Neuroimage* 1998; 8: 229-239
  4. Krakow K, Wieshmann UC, Woermann FG et al. Multimodal MR imaging: functional, diffusion tensor, and chemical shift imaging in a patient with localization-related epilepsy. *Epilepsia* 1999; 40: 1459-1462
  5. Lemieux L, Allen PJ, Franconi F et al. Recording of EEG during fMRI experiments: patient safety. *Magn Reson Med* 1997; 38: 943-952
  6. International Commission on Non-Ionizing Radiation Protection. Medical magnetic resonance (MR) procedures: protection of patients. *Health Phys* 2004; 87: 197-216
  7. Sienkiewicz Z. Rapporteur report: implications for exposure guidelines. *Prog Biophys Mol Biol* 2005; 87: 365-372
  8. Gotman J, Kobayashi E, Bagshaw AP et al. Combining EEG and fMRI: a multimodal tool for epilepsy research. *J Magn Reson Imaging* 2006; 23: 906-920
  9. Gotman J, Pittau F. Combining EEG and fMRI in the study of epileptic discharges. *Epilepsia* 2011; 52(Suppl 4): 38-42
  10. Allen PJ, Josephs O, Turner R. A method for removing imaging artifact from continuous EEG recorded during functional MRI. *Neuroimage* 2000; 12: 230-239
  11. Srivastava G, Crottaz-Herbette S, Lau KM et al. ICA-based procedures for removing ballistocardiogram artifacts from EEG data acquired in the MRI scanner. *Neuroimage* 2005; 24: 50-60
  12. Vanderperren K, De Vos M, Ramautar JR et al. Removal of BCG artifacts from EEG recordings inside the MR scanner: a comparison of methodological and validation-related aspects. *Neuroimage* 2010; 50: 920-934
  13. Salek-Haddadi A, Diehl B, Hamandi K et al. Hemodynamic correlates of epileptiform discharges: an EEG-fMRI study of 63 patients with focal epilepsy. *Brain Res* 2006; 1088: 148-166
  14. Tyvaert L, Hawco C, Kobayashi E et al. Different structures involved during ictal and interictal epileptic activity in malformations of cortical development: an EEG-fMRI study. *Brain* 2008; 131: 2042-2060
  15. Thornton R, Laufs H, Rodionov R et al. EEG correlated functional MRI and postoperative outcome in focal epilepsy. *J Neurol Neurosurg Psychiatry* 2010; 81: 922-927
  16. Alarcon G, Guy CN, Binnie CD et al. Intracerebral propagation of interictal activity in partial epilepsy: implications for source localisation. *J Neurol Neurosurg Psychiatry* 1994; 57: 435-449
  17. Tao JX, Ray A, Hawes-Ebersole S, Ebersole JS. Intracranial EEG substrates of scalp EEG interictal spikes. *Epilepsia* 2005; 46: 669-676
  18. Vulliemoz S, Carmichael DW, Rosenkranz K et al. Simultaneous intracranial EEG and fMRI of interictal epileptic discharges in humans. *Neuroimage* 2011; 54: 182-190
  19. Jann K, Wiest R, Hauf M et al. BOLD correlates of continuously fluctuating epileptic activity isolated by independent component analysis. *Neuroimage* 2008; 42: 635-648
  20. Hesse C, James C. Tracking epileptiform activity in the multichannel ictal EEG using spatially constrained independent component analysis. *Conf Proc IEEE Eng Med Biol Soc* 2005; 2: 2067-2070
  21. Formaggio E, Storti SF, Bertoldo A et al. Integrating EEG and fMRI in epilepsy. *Neuroimage* 2011; 54: 2719-2731
  22. Levan P, Tyvaert L, Gotman J. Modulation by EEG features of BOLD responses to interictal epileptiform discharges. *Neuroimage* 2010; 50: 15-26
  23. Marques JP, Rebola J, Figueiredo P et al. ICA decomposition of EEG signal for fMRI processing in epilepsy. *Hum Brain Mapp* 2009; 30: 2986-2996
  24. Urrestarazu E, Iriarte J, Artieda J et al. Independent component analysis separates spikes of different origin in the EEG. *J Clin Neurophysiol* 2006; 23: 72-78
  25. Grouiller F, Thornton RC, Groening K et al. With or without spikes: localization of focal epileptic activity by simultaneous electroencephalography and functional magnetic resonance imaging. *Brain* 2011; 134: 2867-2886
  26. Michel CM, Lantz G, Spinelli L et al. 128-channel EEG source imaging in epilepsy: clinical yield and localization precision. *J Clin Neurophysiol* 2004; 21: 71-83
  27. Ebersole JS, Wade PB. Spike voltage topography and equivalent dipole localization in complex partial epilepsy. *Brain Topogr* 1990; 3: 21-34
  28. Glover GH. Deconvolution of impulse response in event-related BOLD fMRI. *Neuroimage* 1999; 9: 416-429
  29. Aguirre GK, Zarahn E, D'Esposito M. The variability of human, BOLD hemodynamic responses. *Neuroimage* 1998; 8: 360-369
  30. Re-examination of the evidence for low-dimensional, nonlinear structure in the human electroencephalogram
  31. Moeller F, LeVan P, Gotman J. Independent component analysis (ICA) of generalized spike wave discharges in fMRI: comparison with general linear model-based EEG-fMRI. *Hum Brain Mapp* 2011; 32: 209-217
  32. Kobayashi E, Bagshaw AP, Grova C et al. Negative BOLD responses to epileptic spikes. *Hum Brain Mapp* 2006; 27: 488-497
  33. Hawco CS, Bagshaw AP, Lu Y et al. BOLD changes occur prior to epileptic spikes seen on scalp EEG. *Neuroimage* 2007; 35: 1450-1458
  34. Makiranta M, Ruohonen J, Suominen K et al. BOLD signal increase precedes EEG spike activity – a dynamic penicillin induced focal epilepsy in deep anesthesia. *Neuroimage* 2005; 27: 715-724
  35. Jacobs J, Levan P, Moeller F et al. Hemodynamic changes preceding the interictal EEG spike in patients with focal epilepsy investigated using simultaneous EEG-fMRI. *Neuroimage* 2009; 45: 1220-1231
  36. Moeller F, Siebner HR, Wolff S et al. Changes in activity of striato-thalamo-cortical network precede generalized spike wave discharges. *Neuroimage* 2008; 39: 1839-1849
  37. Osharina V, Ponchel E, Aarabi A et al. Local haemodynamic changes preceding interictal spikes: a simultaneous electrocorticography (ECoG) and near-infrared spectroscopy (NIRS) analysis in rats. *Neuroimage* 2010; 50: 600-607
  38. Spencer SS. Neural networks in human epilepsy: evidence of and implications for treatment. *Epilepsia* 2002; 43: 219-227
  39. Weder BJ, Schindler K, Loher TJ et al. Brain areas involved in medial temporal lobe seizures: a principal component analysis of ictal SPECT data. *Hum Brain Mapp* 2006; 27: 520-534
  40. Federico P, Archer JS, Abbott DF, Jackson GD. Cortical/subcortical BOLD changes associated with epileptic discharges: an EEG-fMRI study at 3 T. *Neurology* 2005; 64: 1125-1130
  41. Kobayashi E, Grova C, Tyvaert L et al. Structures involved at the time of temporal lobe spikes revealed by interindividual group analysis of EEG/fMRI data. *Epilepsia* 2009; 50: 2549-2556
  42. Laufs H, Hamandi K, Salek-Haddadi A et al. Temporal lobe interictal epileptic discharges affect cerebral activity in „default mode“ brain regions. *Hum Brain Mapp* 2007; 28: 1023-1032
  43. Gotman J, Grova C, Bagshaw A et al. Generalized epileptic discharges show thalamocortical activation and suspension of the default state of the brain. *Proc Natl Acad Sci USA* 2005; 102: 15236-15240
  44. Jann K, Dierks T, Boesch C et al. BOLD correlates of EEG alpha phase-locking and the fMRI default mode network. *Neuroimage* 2009; 45: 903-916

45. Zijlmans M, Huiskamp G, Hersevoort M et al. EEG-fMRI in the preoperative work-up for epilepsy surgery. *Brain* 2007; 130: 2343-2353
46. Moeller F, Tyvaert L, Nguyen DK et al. EEG-fMRI: adding to standard evaluations of patients with nonlesional frontal lobe epilepsy. *Neurology* 2009; 73: 2023-2030
47. Lazeyras F, Blanke O, Perrig S et al. EEG-triggered functional MRI in patients with pharmacoresistant epilepsy. *J Magn Reson Imaging* 2000; 12: 177-185
48. Hauf M, Jann K, Schindler K et al. Localizing seizure-onset zones in pre-surgical evaluation of drug-resistant epilepsy by EEG/fMRI: Effectiveness of alternative thresholding strategies. *AJNR Am J Neuroradiol* 2012; accepted
49. Carmichael DW, Thornton JS, Rodionov R et al. Feasibility of simultaneous intracranial EEG-fMRI in humans: a safety study. *Neuroimage* 2010; 49: 379-390
50. Chaudhary UJ, Duncan JS, Lemieux L. Mapping hemodynamic correlates of seizures using fMRI: A review. *Hum Brain Mapp* 2011; Nov 14. doi: 10.1002/hbm.21448. [Epub ahead of print]
51. LeVan P, Tyvaert L, Moeller F, Gotman J. Independent component analysis reveals dynamic ictal BOLD responses in EEG-fMRI data from focal epilepsy patients. *Neuroimage* 2010; 49: 366-378
52. Thornton RC, Rodionov R, Laufs H et al. Imaging haemodynamic changes related to seizures: comparison of EEG-based general linear model, independent component analysis of fMRI and intracranial EEG. *Neuroimage* 2010; 53: 196-205
53. Tyvaert L, Levan P, Dubeau F, Gotman J. Noninvasive dynamic imaging of seizures in epileptic patients. *Hum Brain Mapp* 2009; 30: 3993-4011
54. Hauf M, Slotboom J, Nirkko A et al. Cortical regional hyperperfusion in nonconvulsive status epilepticus measured by dynamic brain perfusion CT. *AJNR Am J Neuroradiol* 2009; 30: 693-698
55. Hauf M, Wiest R, Nirkko A et al. Dissociation of epileptic and inflammatory activity in Rasmussen Encephalitis. *Epilepsy Res* 2009; 83: 265-268
56. Kobayashi E, Hawco CS, Grova C et al. Widespread and intense BOLD changes during brief focal electrographic seizures. *Neurology* 2006; 66: 1049-1055
57. Knowlton RC. Multimodality imaging in partial epilepsies. *Curr Opin Neurol* 2004; 17: 165-172
58. Kurian M, Spinelli L, Delavelle J et al. Multimodality imaging for focus localization in pediatric pharmacoresistant epilepsy. *Epileptic Disord* 2007; 9: 20-31

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### Summary

Visual analysis of EEG signals by clinical experts remains the “gold standard”, but is increasingly complemented by quantitative methods, which offer more objective criteria for assessment and may indicate subtle signal changes possibly escaping even the trained observer’s eye. With regard to the EEG of epilepsy patients two key applications of quantitative EEG (qEEG) analysis methods are early detection or even prediction of seizures and the localization of ictogenic tissue.

qEEG methods can be categorized by the number of signals that are investigated as potentially interacting units (univariate, bivariate, multivariate). In addition, methods can be distinguished by the character of signals or interaction properties (linear or nonlinear). Finally, it can be investigated, whether EEG signals are in a causal relation, thus driving or being driven by others.

In the present article, examples of different qEEG methods as used at the epilepsy unit of the University of Berne are demonstrated by analysing peri-ictal, intracranial EEG. We discuss possible clinical implications and limitations of qEEG methods as well as perspectives for future developments.

patienten bestehen die Hauptanwendungen quantitativer EEG (qEEG) Analysemethoden in der frühen Erkennung oder gar Vorhersage von epileptischen Anfällen sowie in der Lokalisation von iktogenem Gewebe.

qEEG-Methoden können nach der Anzahl der Signale kategorisiert werden, die als möglicherweise wechselwirkende Untereinheiten untersucht werden (uni-, bi- oder multivariat). Weiter kann nach dem Charakter der Signal- oder Wechselwirkungseigenschaften unterschieden werden (linear oder nichtlinear). Schliesslich kann untersucht werden, ob EEG-Signale miteinander in einer kausalen Beziehung stehen, also andere treiben oder von diesen getrieben werden.

Im vorliegenden Artikel werden anhand von peri-iktalem, intrakraniell EEG Beispiele für verschiedene an der Abteilung für Epileptologie der Universität Bern angewendete Varianten der qEEG-Analyse demonstriert. Es wird diskutiert, welche klinischen Rückschlüsse sich aus den Resultaten ziehen lassen. Limitationen sowie Entwicklungsperspektiven quantitativer Analysemethoden werden aufgezeigt.

**Schlüsselwörter:** quantitative EEG Analyse, Epilepsiechirurgie, Netzwerke

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**Key words:** quantitative EEG analysis, epilepsy surgery, networks

### Quantitative Analyse peri-iktaler Vielkanal-EEG-Daten

Die visuelle Analyse von EEG-Signalen durch klinische Experten wird zunehmend erweitert durch die Verwendung quantitativer Methoden. Letztere sollen einerseits objektivere Kriterien bieten und andererseits auch subtile Veränderungen von Signaleigenschaften anzeigen, die selbst dem geschulten Auge möglicherweise entgehen. Im Hinblick auf das EEG von Epilepsie-

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## Analyse quantitative des données péri-ictales de quatre canaux EEG

Les méthodes quantitatives viennent de plus en plus s'associer à l'analyse visuelle de signaux EEG par les experts cliniques. Leur but est de fournir des critères plus objectifs et aussi de mettre en évidence des modifications subtiles dans les caractéristiques des signaux qui peuvent échapper même à l'œil le plus expérimenté. En rapport avec l'EEG de patients épileptiques, les principales applications de méthodes d'analyse quantitative de l'EEG (qEEG) consistent à dépister précocement ou même anticiper des crises épileptiques, ainsi qu'à localiser le tissu ictogène.

Les méthodes qEEG peuvent être classées en fonction du nombre de signaux qui sont étudiés comme sous-entités potentiellement interactives (uni-, bi- ou multivariées). On peut également faire une distinction en fonction du caractère des propriétés du signal ou des effets interactifs. Enfin, on peut examiner une éventuelle relation causale entre les signaux de l'EEG, en d'autres termes, voir s'ils génèrent d'autres signaux ou sont eux-mêmes générés par d'autres signaux.

Dans le présent article sont démontrées à l'appui de l'EEG péri-ictal intracrânien différentes variantes d'analyses qEEG appliquées au département d'épileptologie de l'Université de Berne. Les conclusions cliniques qui peuvent être tirées des résultats sont discutées et l'article met aussi en lumière les limites de même que les perspectives de développement des méthodes d'analyse quantitative.

**Mots clés :** analyse quantitative de l'EEG, chirurgie épileptique, réseaux

### Introduction

Epilepsy is a pathologic state of the central nervous system (CNS) defined by the predisposition to suffer recurrent and unprovoked seizures. As one of the most frequent neurological disorders epilepsy affects roughly 1% of the world population, i.e. approximately 80,000 patients in Switzerland. The most disabling characteristic for epilepsy patients are the seizures, which typically occur suddenly and often without or only with very brief warning signs or symptoms.

In three out of four epilepsy patients seizures can be controlled by anti-seizure drugs [1, 2]. However, in the remainder (approximately 20,000 patients in Switzerland) either combined therapy by multiple drugs is ineffective or the unwanted side effects of the medication cannot be tolerated. For these patients epilepsy surgery [1] is an option that should be evaluated. It is estimated that up to 50% of the target group might benefit from surgical epilepsy therapy [3], which is possible when the seizure onset zone (SOZ) consists of a clearly circumscribed brain area that can be removed without

causing unacceptable neurological deficits (i.e. the SOZ is not part of so-called "eloquent cortex"). Epilepsy surgery is a complex intervention requiring interdisciplinary diagnostic workup by neurologists, neuroradiologists, neuropsychologists and neurosurgeons.

Seizures are often considered to be due to pathological changes of synchronization of the electrical activity of large groups of nerve cells. The collective synchronous synaptic potentials and intrinsic currents of nerve cells are measurable by electroencephalography (EEG; [4, 5]) on the scalp or inside the cranium under favorable conditions. Most importantly, electrical activity of many neurons must be oriented into the direction of the measurement electrode in order to cause fluctuations of electrical potentials large enough to be detected in several millimeters or centimeters distance. This poses certain limitations, especially on scalp EEG, which is particularly sensitive to events on the top of gyri but detects electrical signals generated in deep brain structures with much reduced sensitivity. Notwithstanding these limitations the EEG continues having high diagnostic value in epilepsy patients.

In pre-surgical evaluation for epilepsy surgery patients suffering from pharmacoresistant focal-onset seizures first undergo continuous scalp video-EEG monitoring (so-called "phase I") for 1-3 weeks, until several seizures have been recorded. If the clinical and EEG seizure characteristics from phase I are reproducible and in agreement with complementary information as e.g. from high resolution magnetic resonance imaging (MRI), and there are no indications for serious post-surgical neurological deficits the decision about epilepsy surgery may be made already at this stage. If, however, there are inconsistencies, video-EEG monitoring with intracranial electrodes (so-called "phase II") is required. Here, electrodes are implanted directly onto or into the brain using strip, grid or depth electrodes (**Figure 1**). Advantages of intracranial EEG (iEEG) is the much better signal to noise ratio and the better spatial resolution (~1cm<sup>2</sup> as compared to >10cm<sup>2</sup> for scalp electrodes). However, intracranial electrodes cannot be distributed equally over the whole cortex, thus limiting spatial sampling. Therefore, a good working hypothesis about the localization of the SOZ is required, which can then be tested by a few intracranial electrodes with roughly 30-150 contacts in total. In order to minimize the risk of complications [6], phase II monitoring is often discontinued after several days, thereby potentially limiting the number of recorded seizures to only a few.

The gold standard of EEG interpretation is still visual analysis by trained epileptologists. This classic analysis method basically consists in careful pattern recognition and additional integration of diverse clinical background information. Therefore visual EEG interpretation strongly depends on the experience and at least partly on the subjective interpretation of the individual expert. In addition, visual analysis of iEEG may be made difficult by the large number of signals (up to an order

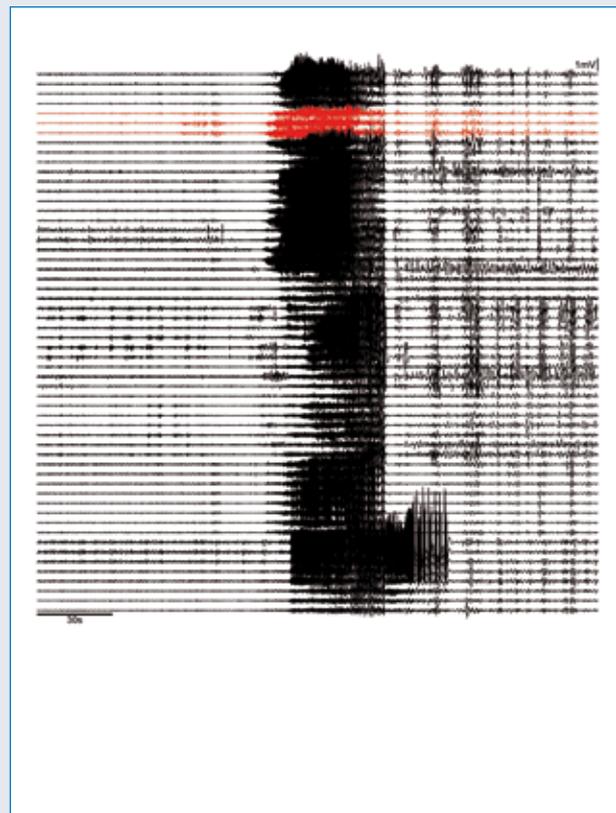
of magnitude more than for standard scalp EEG). For these reasons visual EEG analysis is increasingly complemented by quantitative EEG (qEEG) analysis, which uses methods developed in mathematics and physics to interpret the EEG more objectively. In the present article qEEG methods are reviewed with special focus on those developed and applied by our research groups.

Currently the main applications of qEEG in epileptology are the following. Early seizure detection [7] may have implications for closed loop intervention systems with the aim of early seizure abortion [8]. Seizure prediction has been a very stimulating goal for the development of qEEG algorithms in the last 15 years. Despite considerable effort, not a single seizure prediction algorithm has so far proven effective in the sense that it outperforms a random predictor in terms of sensitivity and specificity [9-11]. Other – and probably the more promising – applications of qEEG are to reliably localize and delineate the seizure onset zone during pre-surgical diagnostic evaluation.

## Signal characteristics assessed by qEEG

Before elaborating in more detail on different qEEG analysis methods we here list some prominent signal characteristics that may be assessed.

- Epileptic discharges produce *fast* signals and *steep* wave forms, which may be strongly localized or propagate over large brain areas. Thus, unraveling high frequencies or steep wave forms may help to localize the origin of epileptic activity.
- In contrast to normal background brain activity epilepto- or ictogenic processes have long been assumed to be associated with strong *nonlinearities* [12, 13] or even low dimensional deterministic *chaos* [14]. Consequently, qEEG measures that sensitively and reliably detect nonlinear signal properties may add relevant diagnostic information to visual analysis, which often is strongly biased by linear characteristics (amplitude and frequency distribution, temporal co-evolution of large amplitudes).
- Epileptic brain activity has been conjectured to be more *deterministic* than normal background activity. Certain qEEG measures quantify the degree of determinism and therefore may help to separate more



**Figure 1:** (color) a) X-ray of a 27 year old male epilepsy patient with intracranial EEG electrodes implanted. Five strip electrodes (temporo-polar, temporo-lateral-basal, fronto-central-temporal, fronto-orbital and fronto-polar, all on the left hemisphere) and two depth electrodes in both hippocampi were used. The total number of contacts was 56. b) EEG recording containing a focal onset seizure starting in the pole of the left temporal lobe. The contacts recording from the SOZ in panel a and the corresponding signals (panel b) are colored in red. The patient became seizure free after surgical removal of the pole of the left temporal lobe.

deterministic from more noise dominated brain areas or temporal epochs.

- The human brain is one of the most complex known *networks*. In nerve cells information is integrated via conditional generation of action potentials and information is exchanged via propagation of electrical excitation along axons and dendrites. While the anatomy of the brain network can be investigated non-invasively by magnetic resonance imaging (MRI) techniques, its functional aspects can be revealed by qEEG and fMRI.
- To reconstruct functional networks *interrelation* measures are used that quantify the degree of association between EEG signals. These measures can or cannot be sensitive to nonlinear effects. In addition, the measures can be asymmetric, thus indicating causal or driver-responder relations.
- For all the signal characteristics mentioned before special attention may be put onto *temporal progressions* and *spatial pathways*. Brain areas that are involved early in the epileptic process may play a more important role for seizure generation than those involved late. Similarly, information about critical parts of the network (so-called “hubs”) that spread focal ictal brain activity over larger areas may be considered for planning of epilepsy surgery.

## Systematics of qEEG

Methods of qEEG analysis may be subdivided in several ways. After briefly sketching a systematic classification of qEEG analysis algorithms we give several examples, which will be illustrated using the iEEG of **Figure 1**.

One possible classification is by the number of EEG signals that are considered as hypothetically independent sub-units (**Figure 2**). *Univariate* methods treat every channel as if it was completely isolated from all the other channels. *Bivariate* methods aim at characterizing the interrelation between pairs of EEG channels. Finally, *multivariate* methods treat all EEG channels and their interactions as a whole.

This subdivision runs parallel to the assessed *spatial scale*. *Univariate* measures inform about the electrical activity beneath a single EEG contact (smallest spatial scale accessible by current iEEG macro-electrodes). In contrast, certain *multivariate* techniques integrate properties of the whole observed system, therefore assessing the largest accessible spatial scale. Other *multivariate* techniques inform about processes taking place at intermediate spatial scales.

Another categorization is by linear versus nonlinear methods, which can fall into either of the above mentioned groups. *Linear* algorithms are suited for description of situations where input and output of a system are proportional, whereas *nonlinear* algorithms are more general in the sense that no (or less

strict) a priori assumptions are made.

Lastly, interrelation measures can be symmetric or directional. *Directional* interrelation measures allow to assess if one signal is driving or being driven by the other. *Symmetric* measures assess exclusively the overall degree of interaction.

## Examples for a peri-ictal iEEG recording

### Univariate measures

The most common univariate, linear qEEG method is power analysis. It is implemented in almost every EEG viewer, where selected pieces of EEG can be decomposed into their spectral content using the Fourier transform. Results of power analysis can either be displayed as the distribution of signal power over the whole frequency range or – in coarser grained manner – as the total power in the classical frequency bands (delta, theta, alpha, beta, gamma). In **Figure 3a** the power spectra for two epochs of the same iEEG channel of **Figure 1b** are shown. Power roughly depends on frequency like  $P(f) \sim f^\nu$  with  $1 < \nu < 2$  [15]. The signal recorded shortly after seizure onset (blue) shows a pronounced peak in high frequencies  $60\text{Hz} < f < 100\text{Hz}$ , which is a typical sign of early ictal EEG activity. Before seizure this peak is absent (red).

During seizures large networks of neurons change the synchronization of their electrical activity. The measurable EEG is affected by showing “epileptiform activity”, which implies either high amplitudes or high frequencies or both. A simple measure that increases in all these situations is the absolute value of the temporal derivative of the EEG signals. Schindler et al. [16, 17] used the EEG “slope” to detect epileptic seizures in a more objective manner than by visual analysis. Similar measures were used in [18, 19]. **Figure 3** shows a comparison of the power spectra of original (panel a) signals and their temporal derivative (panel b). Due to elementary properties of the Fourier transform the spectrum of the derivative is much more flat than for the original signals (“spectral whitening”). As compared to the original EEG, where the high frequency peak recorded after seizure onset is suppressed in power by at least one order of magnitude, it constitutes the prominent peak on top of the whitened signals.

For the iEEG of **Figure 1** the temporal evolution of the absolute EEG slope as compared to a pre-ictal reference epoch is shown in **Figure 4**. In panel b “epileptiform” activity is displayed in black and “normal” activity in white. Channel TPL6 recording from the pole of the left temporal lobe shows epileptiform activity more than 30 seconds earlier than the remainder, which follow a clearly visible temporal progression. Also noteworthy is that in contrast to initiation epileptiform activity ceases at the same time in almost all channels.

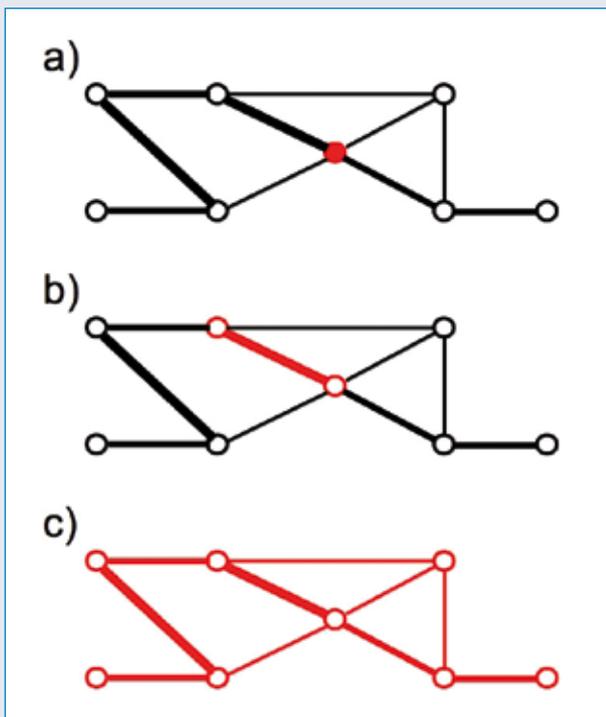


Figure 2: (color) Schematic representation of a complex network. Nodes (number  $M=8$  in the example) are drawn as open circles and links as lines with thickness indicating interaction strength. a) Univariate measures treat every node as if it was isolated from the rest of the network. There are  $M$  possibilities to select a node. b) Bivariate measures investigate the link between a pair of nodes. Influences from the remainder of the network are neglected. The number of node pairs is  $M(M-1)/2$ . c) Multivariate measures aim at treating the network as a whole, integrating information from all nodes and all links. Global multivariate measures are characterized by a single number for the whole network. However, there exist options to assign local multivariate properties also to single nodes or links.

This becomes clear from the asymmetry in the profile of panel a showing the number of channels recording epileptiform signals. The rise of this number between seconds 30 and 50 is much slower than the abrupt drop near second 80.

In [20] the absolute EEG slope has been used to show that clinically “generalized” seizures not necessarily exhibit epileptiform activity on all channels. Remarkably, this was true despite using intracranial EEG electrodes, which were implanted onto a limited cortex area based on a previous hypothesis about the SOZ. In conclusion, even during “generalized” seizures EEG may not be epileptiform in all brain areas.

The measures discussed so far were all linear. We now briefly address nonlinear univariate measures based on the theory of nonlinear dynamical systems and low dimensional chaos [21, 22]. More comprehensive reviews of EEG applications are given in [23, 14, 24, 25]. According to Takens’ theorem [26] the space in which a nonlinear dynamical system evolves (“phase

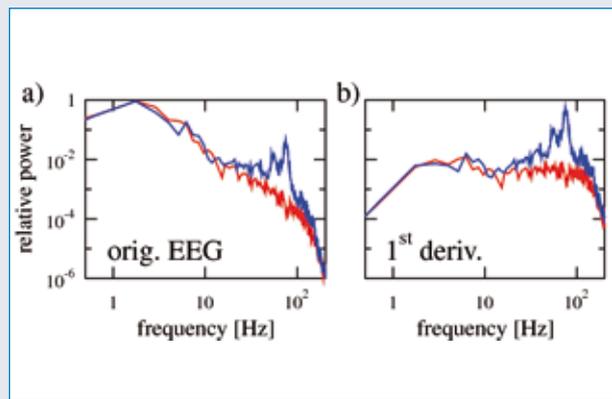


Figure 3: (color) Distribution of signal power over the frequency spectrum for two sections of the iEEG shown in Figure 1. Pre-ictal (red) and early ictal (blue) epochs (length=8s) of channel TPL6 recording from the SOZ located in the pole of the left temporal lobe are shown on log-log-scale. a) result for the original iEEG signal, b) result for the first temporal derivative (“slope”).

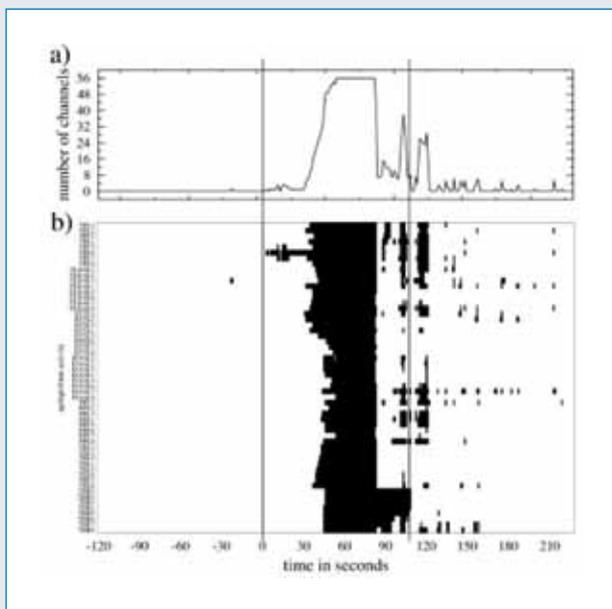


Figure 4: Analysis of the signal slope. a) Total number of channels and b) channels showing epileptiform EEG activity for the data of Figure 1. According to [17] deviations of more than 2.5 standard deviations from a pre-ictal reference segment are classified as epileptiform (black) and as normal otherwise. The bars at the left and right margin of panel b mark the brain area that has surgically been removed in this patient.

space”) can in principle be reconstructed from univariate time series. A class of time series analysis methods exploits this theorem and consecutively quantifies properties of the reconstructed attractor. One quantifier that has extensively been applied to qEEG analysis is the correlation dimension and derived measures [27-29], which were used to interpret EEG as showing signs of low dimensional chaos under certain circumstances.

However, after careful re-examination by the same authors, the results of [27] turned out to be not significant [30]. Similar problems were encountered for other analyses.

Another nonlinear way to handle univariate time series is by symbolic analysis. In this class of methods the full information content of the data is coarse grained by deriving a finite (most often a small) number of “symbols” and analyzing their frequency distribution statistically. Consequently, the degree of abstraction of this class of methods is rather high at first sight. On the other hand there is analogy between visual EEG analysis and a special class of symbols, the so called “ordinal patterns”. In both approaches certain wave forms are characterized [31]. To be specific, when analyzing ordinal patterns  $d$  consecutive EEG samples are rank ordered and symbols are defined by the sequence of ranks. For instance, for  $d=3$  the symbol “123” (“321”) would indicate a monotonous increase (decrease) and “132” a local maximum. The number of symbols of length  $d$  is  $d!=d*(d-1)*...*2*1$ . For Gaussian white noise all symbols are equally likely. In contrast, deterministic dynamics follows an intrinsic rule and the distribution of patterns becomes non-uniform such that in a sample of length  $L \gg d$  some ordinal patterns may not appear at all (“forbidden”). Thus, experimental observation of forbidden ordinal patterns can be interpreted as an indicator of deterministic dynamics [32, 33]. To exclude the possibility of observing forbidden ordinal patterns by chance, comparison with surrogates [34] is mandatory.

In [31] forbidden ordinal patterns have been analyzed for peri-ictal iEEG. An example of this analysis for the iEEG of Figure 1 is given in Figure 5. Before seizure the fraction of forbidden patterns  $n_{fp}$  is in the range 0.5 ... 0.6, indicating that the iEEG signals are much more deterministic than white noise (panel A), which contains no forbidden ordinal patterns. During seizure the fraction of forbidden patterns increases in channels 1 to 16 (contacts on strip electrodes recording from the left temporal lobe) and 41 to 56 (depth electrodes placed in both hippocampi), reflecting increased ictal determinism in these signals. In panel B the time course of channel 6 is compared to the mean over all channels, which undergoes a maximum and then settles at a lower level. Determinism globally increases during seizure and is reduced in the post-ictal time period. The contribution to these changes is not equally distributed.

Another class of symbols are “bit-strings”, i.e. sequences of zeroes and ones (e.g. 00101) that encode certain signal properties as for example whether the EEG amplitude increases (“1”) or decreases (“0”) from one time step to the next. An advantage of bit-strings over ordinal patterns is that for the same length  $d$  of used data the space of possible symbols is (much) smaller:  $2^d$  for bit-strings as compared to  $d!$  for ordinal patterns; for  $d=5$  this difference is 32 vs. 120 and for  $d=10$  it is 1024 vs. 3,628,800. In the context of qEEG of

epilepsy patients bit-string (also called “binary”) analysis is still rare.

### Bivariate measures: symmetric

Next we discuss applications of bivariate interrelation measures to qEEG analysis. One of the most classic quantifiers for data association is Pearson’s cross-correlation coefficient [35]. It evaluates the co-variation of two data sets or time series and tends to values close to zero for uncorrelated data sets. For identical data sets its value is 1 and -1 for data sets that are identical up to a sign, i.e. that are “anti-correlated”. Cross-correlation is best visualized by plotting the second data set (Y) against the first (X) after subtracting the mean and normalizing to unit variance. In Figure 6a this is shown for the neighboring channels TPL6 and TPL7 of the iEEG in Figure 1 (cross-correlation coefficient  $CC=0.771$ ). For data sets with Gaussian amplitude distribution the lines of equal density are ellipses. Correlation is indicated by ellipses with unequal half axes, such that data points accumulate along one diagonal. In contrast, circular distributions result for uncorrelated data.

Mutual information [36, 37] is another interrelation measure that quantifies the shape of the joint probability distribution of two data sets. It is an entropy based measure for deviations from statistical independence (i.e. data sets whose joint probability distribution is given by the product of the marginal distributions) and can be normalized, such that it assumes values between 0 for independent data and 1 for identical data (up to a sign). In Figure 6b the marginal amplitude histograms are shown for the normalized signals of Figure 6a. Assuming statistical independence the joint probability histogram would be the one of Figure 6c. The considerable deviation of the true joint probability histogram (Figure 6d) from the product rule gives rise to a large mutual information coefficient (normalized mutual information  $NMI=0.926$ ). The advantage of mutual information over the linear Pearson’s cross-correlation is that it is sensitive to any deviation from the product rule, including curvilinear density distributions as e.g. for the case  $Y=X^2$ , the simplest association that is completely missed by cross-correlation ( $CC=0$ ,  $NMI=1$ ).

### Bivariate measures: directed

A variety of interrelation measures aim to quantify not only the overall strength but also the direction of couplings between nonlinear dynamics. These measures include nonlinear Granger causality [38], transfer entropy [39, 37, 40], phase dynamics measures [41], as well as so-called nonlinear interdependence measures ([42] and references therein). The latter operate in the reconstructed phase spaces of the dynamics X and Y (see above). Similar states in X or Y will be spatially

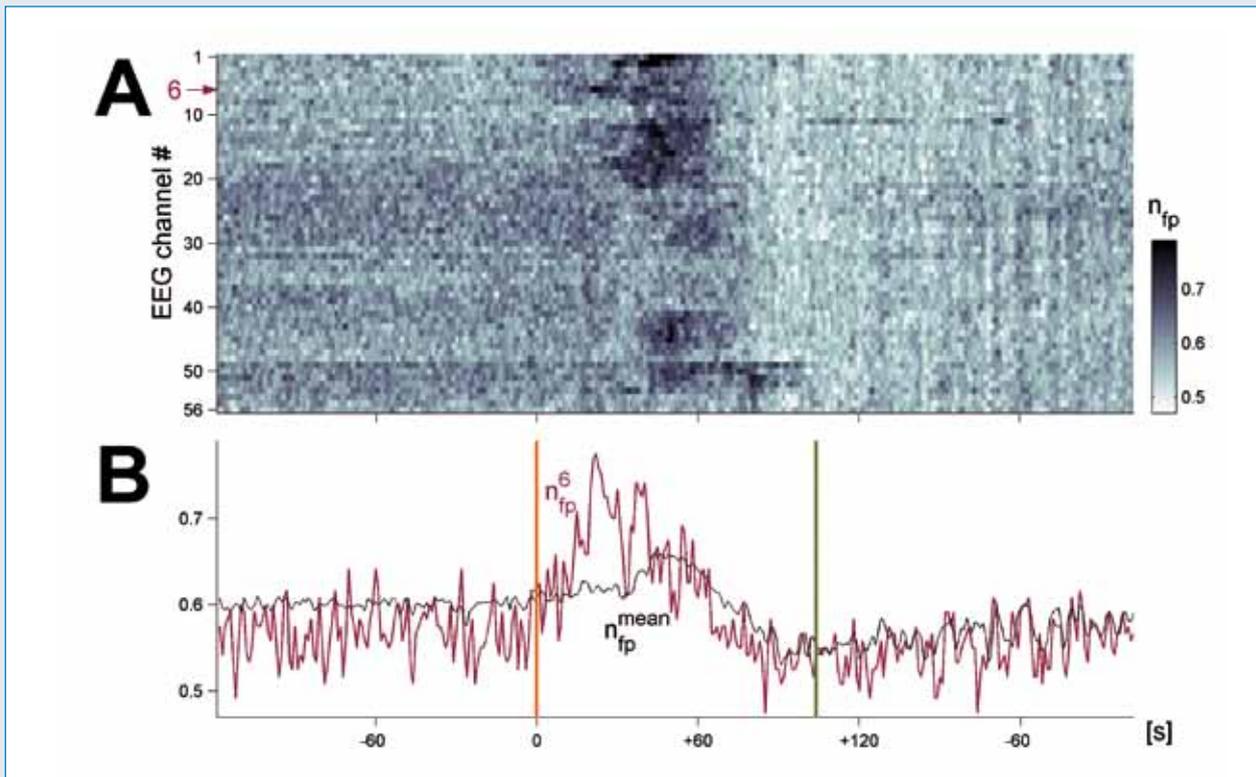


Figure 5: Symbolic analysis of the iEEG data of Figure 1 using word length  $d=5$  and  $T=1024$  temporal samples. a) Gray-scale representation of the fraction of forbidden patterns  $n_{fp}$  for each iEEG channel (number normalized to the total number of ordinal patterns  $d!$ ). b) Comparison of  $n_{fp}$  for channel 6, which shows first increase to the average.

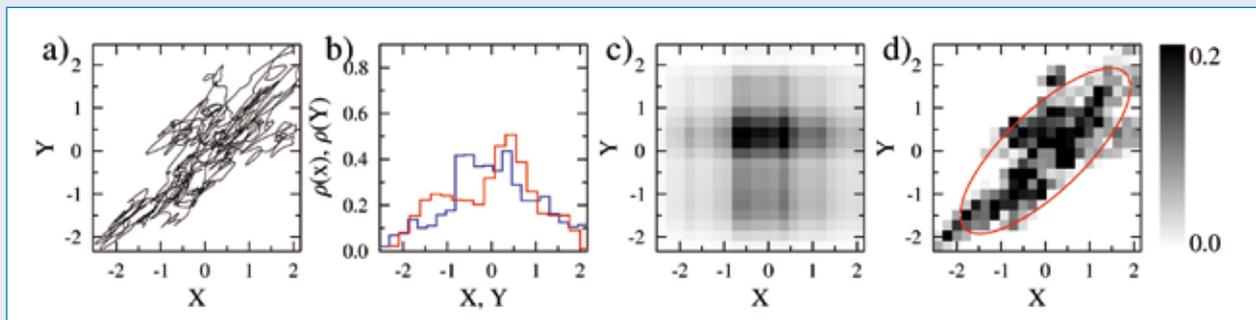


Figure 6: (color) Illustration of Pearson's cross-correlation coefficient and mutual information at the example of two seconds iEEG (center of the early ictal segment used in Figure 3). a) Trajectory of the iEEG amplitude in the space spanned by contacts TPL6 and TPL7 recording from the SOZ. b) Histograms of the amplitude distributions of both signals. c) Two-dimensional histogram as expected for the joint probability distribution of statistically independent signals with given amplitude distribution. d) Joint probability histogram that is actually derived from the data. The deviation of the distribution shown in d) from c) is quantified by normalized mutual information ( $NMI=0.926$ ). Pearson's cross-correlation coefficient ( $C=0.771$ ) describes the best fit of the data by an ellipsoid density distribution centered at the origin (red).

close in the respective phase spaces. Suppose that we have a unidirectional coupling from X to Y. As a result of this coupling, states in the driving dynamics X that are simultaneous to similar states in the driven dynamics Y are on average closer than expected under the assumption of independence. The opposite holds true only to a weaker degree, i.e. closeness in the driving dynamics X not necessarily implies closeness in the driven dynamics Y. Nonlinear interdependence measures exploit this

asymmetry to determine the direction of couplings.

Here we show exemplary results for a specific nonlinear interdependence measure, termed L, which was shown to be of higher sensitivity and specificity for directional couplings than a number of related earlier approaches [42]. Figure 7 shows results of a moving window analysis of the peri-ictal recording depicted in Figure 1. During the initial phase of the seizure ( $16s < t < 56s$ ) some off-diagonal elements of the inter-

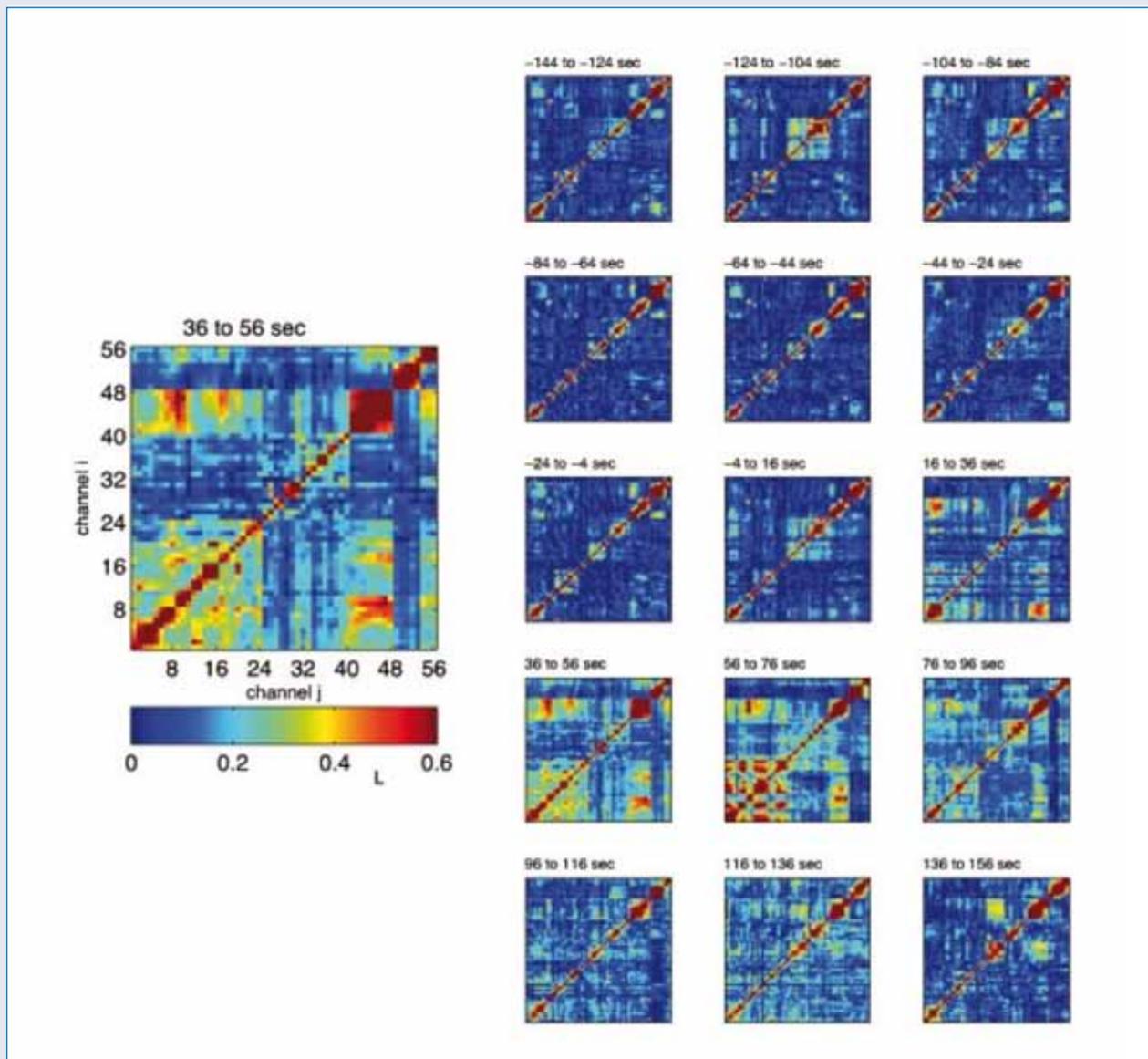


Figure 7: Results of a moving window nonlinear interdependence measure analysis. Each matrix shows results obtained from a window of 20 seconds length. The seizure lasts from  $t=0s$  to  $t=107s$ . Within individual matrices, high  $L$  values in the  $i$ -th row and  $j$ -th column indicate a strong nonlinear interdependence in the direction from channel with index  $i$  to the channel with index  $j$ . The asymmetry of these matrices can be interpreted as follows: A positive difference,  $L(\text{row } i, \text{column } j) - L(\text{row } j, \text{column } i)$ , indicates that the predominant direction of the coupling is from channel with index  $i$  to the channel with index  $j$ . For a more thorough discussion of the interpretability of these values please refer to Andrzejak et al. [52] and Chicharro & Andrzejak [42].

relation matrix gradually increase. In this epoch the most prominent off-diagonal matrix elements connect channels 1 to 8 (pole of the left temporal lobe, SOZ) with channels 41 to 48 (depth electrode in the left hippocampus). Later ( $56s < t < 76s$ ) the coupling between the SOZ and temporo-lateral-basal contacts (channels 9-16) and fronto-central contacts (channels 17-25) becomes more dominant. The deviation from strict symmetry indicates driver-responder relationships. Especially before the seizure the coupling from the SOZ to the depth electrodes (channels 41-56) appears larger than in the opposite direction.

Without going into details an overview of some of the most prominent univariate and bivariate, linear

and nonlinear measures that have already been used for qEEG analysis is given in **Table 1**. For many bivariate measures in addition “partial” versions exist, which account for indirect effects. For example, the value of partial cross-correlation [43] is close to the value of Pearson’s cross-correlation if two signals  $X$  and  $Y$  are directly interacting. In contrast, partial correlation is much smaller than Pearson’s coefficient if  $X$  and  $Y$  are interacting via a third signal  $Z$  only. Note, the fact that partial interrelation measures only account for observed signals, may be a serious limitation for iEEG, where one is always confronted with incomplete spatial sampling and unobserved activity, which may be responsible for signal associations. Another problem may arise when

too many “third” signals  $Z_1 \dots Z_N$ , ( $N \gg 1$ ) are offered as possible pathways for indirect interrelation. In this case, the system may be “over-fitted” and direct effects may erroneously be attributed to indirect interaction.

## Multivariate approaches

Multivariate approaches treat all observed EEG channels and their interactions as a whole. In the following we discuss two classes of multivariate qEEG analysis, both operating on interrelation matrices that were previously defined using bivariate measures. In **Figure 8** examples are given for different interrelation matrices evaluated from the same section of intracranial EEG (length two seconds, 2048 temporal samples). The peri-ictal evolution of interrelation matrices (for a directed measure see **Figure 7**) can be highly complex, making methods for information condensation desirable.

## Multivariate measures based on matrix diagonalization

Interrelation matrices  $\mathbf{C}$  can be interpreted as mappings between vectors in the space spanned by the data channels. Vectors that are mapped onto themselves represent special cases, which can be used to define a mathematically distinguished basis. This basis can be found by solving the matrix equation  $\mathbf{C} \mathbf{v} = \lambda \mathbf{v}$ . The *eigenvalues*  $\lambda$  can be used to quantify the total interrelation in the system (largest spatial scale accessible by EEG), whereas the *eigenvectors*  $\mathbf{v}$  give information about the contribution of the channels to interrelation patterns (intermediate spatial scale).

For real-valued symmetric matrices  $\mathbf{C}$  (as resulting from symmetric interrelation measures, e.g. cross-correlation or mutual information) the eigenvalues are real numbers that can be rank ordered. The sum of all eigenvalues is identical to the sum of the diagonal elements of  $\mathbf{C}$ , which for normalized measures is equal to the number of channels. A direct consequence is that finite off-diagonal matrix elements  $|C_{ki}| > 0$  lead to an increase of large eigenvalues  $\lambda$ , which is compensated by a decrease of small eigenvalues (“repulsion”; [44]). Relevant information is confined to the repelled eigenvalues and corresponding eigenvectors, whereas the central ones are compatible with Random Matrix Theory (RMT; [45, 44]). First application of eigenvalues of the cross-correlation matrix to peri-ictal iEEG was made by Schindler et al. [46, 17], finding that seizures are not per se highly correlated events. Rather, correlation increases continuously (or even decreases first) and seizures as well as status epilepticus stop when correlation is large.

The value of Pearson’s cross-correlation coefficient is greatly influenced by the signals’ power spectra and

the amount of data used for its estimation. In Müller et al. [47] eigenvalue repulsion was exploited to define a measure of “genuine” cross-correlation strength (CCS) to which only significantly repelled eigenvalues of the cross-correlation matrix contribute. The measure of total correlation strength (TCS) integrates all eigenvalues and random correlation strength (RCS) is the same for uncorrelated surrogate data in place of the original data. It was demonstrated that TCS and RCS are sensitive to dynamical changes of the signals’ power spectra even though the interaction was kept constant. In contrast, CCS is almost exclusively sensitive to changes in signal interaction [47]. First application of CCS to epileptic EEG was made in Müller et al. [48]. For focal onset seizures as assessed by scalp EEG it was found that during and after seizure CCS decreases significantly for broadband and low frequency data (below 12.5 Hz). In agreement with recently published results [49] these findings may be interpreted as ictal fragmentation of functional networks.

In Rummel et al. [50] the concept was generalized to TCS, CCS and RCS *matrices*, with only significant matrix elements retained. An example for the cross-correlation and the CCS matrix of pre-ictal iEEG data is shown in **Figures 8a and b**, respectively. The CCS matrix is much sparser than the original cross-correlation matrix. Extension to the nonlinear interrelation measure of mutual information was made in Rummel et al. [51]. A combination of linear and nonlinear interrelation measures with univariate and multivariate surrogates [34] enables separation of significantly nonlinear (i.e. interrelation that cannot be explained by linear effects alone) from entirely linear interrelation. In agreement with earlier results [12, 13, 52] preliminary application to intracranial EEG suggests that nonlinearities are more pronounced ictally than interictally and that epileptogenic tissue generates electrical signals with stronger nonlinear characteristics than non-epileptogenic tissue [51].

As discussed earlier, the temporal derivatives of EEG signals may be used to identify channels with epileptiform activity. This suggests to combine temporal differentiation with correlation analysis. In **Figure 8c** the slope cross-correlation (SCC) matrix is shown and in **Figure 8d** only significant elements are retained. The average level of correlation is smaller for the temporal derivatives and anti-correlation is almost absent. An advantage of **SCC** is that fluctuations are much smaller than for Pearson’s coefficient. As a consequence eigenvalues of SCC matrices are much more stable in time [Rummel et al., unpublished]. In **Figure 9a** the peri-ictal evolution of TCS calculated from the **SCC** matrix is shown for the iEEG of **Figure 1**. Pre-ictally the total correlation in the system is remarkably stable. The seizure manifests itself by a pronounced increase of TCS 30 seconds after seizure initiation, i.e. at the time of seizure spreading, cf. **Figure 4**. In agreement with the findings by Schindler et al. [46, 17] the seizure terminates

**Table 1:** Overview of prominent univariate and bivariate measures used in qEEG analysis.

	univariate	bivariate
linear	<ul style="list-style-type: none"><li>• power spectrum</li><li>• auto-correlation</li><li>• statistical moments of amplitude or power distributions</li><li>• Hjorth mobility</li><li>• signal slopes</li></ul>	<ul style="list-style-type: none"><li>• Pearson's cross-correlation</li><li>• cross-spectrum</li><li>• coherence</li><li>• Granger causality</li></ul>
nonlinear	<ul style="list-style-type: none"><li>• (effective) correlation dimension</li><li>• Lyapunov exponents</li><li>• Poincaré sections</li><li>• nonlinear prediction error</li><li>• local flow</li><li>• algorithmic complexity</li><li>• forbidden ordinal patterns</li></ul>	<ul style="list-style-type: none"><li>• nonlinear correlation coefficient</li><li>• phase synchronization</li><li>• mutual information</li><li>• transfer entropy</li><li>• synchronization likelihood</li><li>• event synchronization</li><li>• nonlinear interdependence measures</li></ul>

when correlation is largest. In panel b relative changes of the channels' contribution to the eigenvector  $\mathbf{v}_m$  corresponding to the largest eigenvalue  $\lambda_m$  are displayed. In channels showing early epileptiform activity in **Figure 4** the relative contribution to  $\mathbf{v}_m$  drops significantly (blue), whereas for channels with late onset of epileptiform activity the opposite is true (red). This can be interpreted as a spatial rearrangement of functional interactions within the system, which even persists after seizure termination.

### Multivariate measures based on graph theory

An alternative multivariate approach is based on graph theory, see [53-56] for reviews. In this context, the signals recorded from EEG electrodes are interpreted as nodes and links between nodes are defined by interrelation measures. Presence or absence of a link between a pair of nodes is defined by the *adjacency matrix*, which has only elements "0" (no link) or "1" (link present). For binary graphs only the topology of the system is analyzed and therefore the adjacency matrix is the only relevant entity. Based on interrelation matrices the adjacency matrix may most easily be constructed by defining a threshold and setting all elements whose modulus exceeds the threshold to 1 and to 0 otherwise. A more sophisticated procedure is to use link specific thresholds, as e.g. done for determining the elements of the CCS matrix [50] or independently in [57].

Graphs can be analyzed by measures that focus on local and global properties. The most prominent measure for local properties is the *clustering coefficient*. The clustering coefficient of each node X quantifies the

fraction of neighbors Y and Z that are also directly connected. Global network properties can be measured by *shortest path lengths or efficiencies*. The efficiency of node X measures how easily all other nodes can be reached from X. The whole network's efficiency (or clustering coefficient) is the average over all node efficiencies (or clustering coefficients). Another important class of graph measures are the *betweennesses*. Node and link betweennesses quantify the fraction of shortest paths running through a particular node or link. Most graph measures sensitively depend on the link density. Therefore it is advisable to report their values relative to suitably randomized networks.

Measures from graph theory have increasingly been applied to EEG data of epilepsy patients in the last five years, see e.g. [58-62]. We here restrict ourselves to a single illustrative example. The binary graph representation of the CCS matrix of **Figure 8b** is shown in **Figure 10**, where all connected nodes are drawn as ellipses and links as lines. All node efficiencies are smaller than those of randomized networks and individual deviations are displayed as gray shadings. The network falls into four sub-graphs, of which two are trivial. The link density is largest in the strip electrode on the pole of the left temporal lobe (TPL) and the depth electrodes (TEL, TER). Interestingly, the connectivity between TPL and TER is high and stems from significantly anti-correlated signals (**Figure 8b**), whereas TPL and TEL are connected by only a single link, which in consequence has very high link betweenness as well as vulnerability (i.e. the network is significantly changed by removal of this link).

In addition to binary graphs the concept of weighted graphs exists, where the full interrelation matrix is

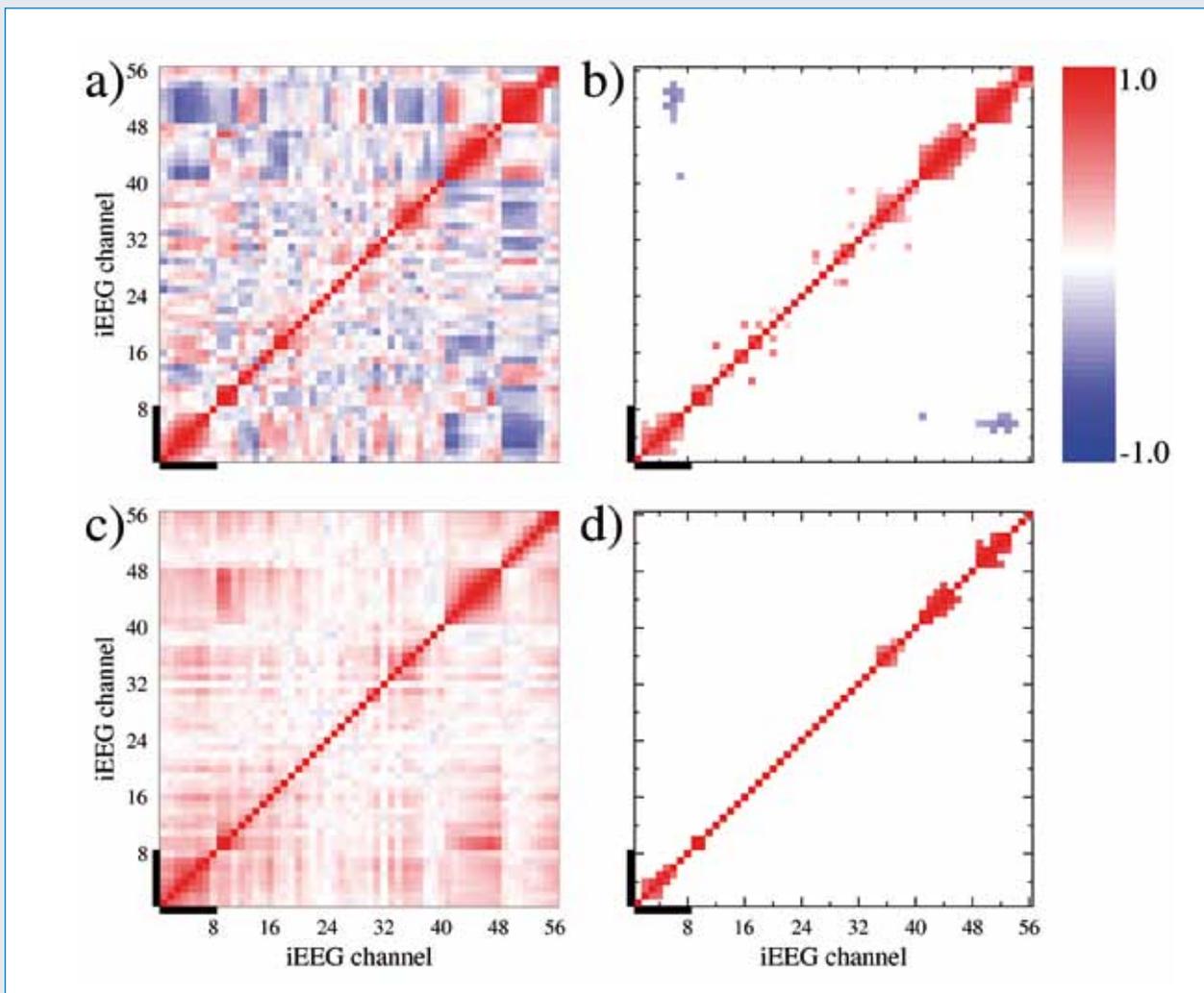


Figure 8: (color) Examples of different interrelation matrices for the same pre-ictal iEEG epoch of two seconds length. a) cross-correlation matrix, b) CCS matrix of [50], c) slope cross-correlation matrix of [53], d) CCS matrix based on slope cross-correlation.

interpreted on basis of graph measures. Also, graphs do not need to be symmetric in the sense that all links are bi-directional. Rather, in directed graphs links can be uni-directional, meaning that information can be transferred only from node X to node Y but not the other way.

### Summary and discussion

The development of qEEG analysis methods has been strongly promoted by the goal of seizure prediction over the last 15 years. Despite initial euphoria, so far this problem could not be solved [9-11]. The fact that prediction algorithms at the same time have to be highly sensitive (to avoid that seizures are missed) and specific (to avoid false alarms that expose patients to stress) remains challenging. After all, reliable seizure prediction algorithms have to announce a very large fraction of seizures with sufficient warning time, while

the time under false warning must be minimal. It remains questionable whether these requirements can be met in future.

Despite disappointing results with regard to seizure prediction qEEG analysis has generated many promising approaches towards the problems of more objective lateralization and localization of epileptogenic brain areas, some of which have been reviewed in the present article. As illustrated at the example of a peri-ictal iEEG recording, the ictal dynamics of many complementary qEEG measures characterize the same brain region as epileptogenic in this patient (pole of the left temporal lobe, iEEG channels TPL5-TPL7, see **Figure 1**). After surgical removal of this brain region the patient has become seizure free for more than two and a half years. Regarding univariate properties the power spectrum and absolute slope reveal high frequency components on these channels, which are much less pronounced in the remainder (**Figures 3 and 4**). A symbolic dynamic approach counting forbidden ordinal patterns shows

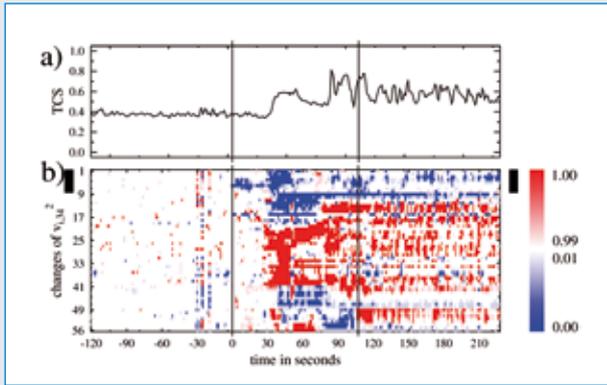


Figure 9: (color) Peri-ictal dynamics of measures derived from the eigenvalues and eigenvectors of the SCC matrix for the data of Figure 1. a) total correlation strength (TCS). b) significant deviations of the squared components of the largest SCC eigenvector from a pre-ictal reference epoch starting five minutes and ending three minutes before seizure onset. The bars at the left and right margin of panel b mark the brain area that has surgically been removed in this patient.

first ictal changes on the same channels (Figure 5). Similarly, a bivariate directed measure detects the earliest and most prominent off-diagonal interrelations between channels 1-8 and the ipsi-lateral depth electrode (channels 41-48, see Figure 7). Multivariate quantifiers localize the first and most pronounced alterations in signal interaction to the pole of the left temporal lobe (Figure 9). Interestingly, correlation of iEEG slopes of these channels *decreases* significantly at seizure onset, i.e. in a region and epoch where neuronal cooperativity (as e.g. assessed by large signal power in high frequency components or large signal slopes) *increases*. This indicates a significant reorganization of functional networks in the course of epileptic seizures [49]. Measures based on graph theory have also been briefly illustrated (Figure 10).

Notwithstanding the achievements of qEEG analysis tools, there remain several limitations and pitfalls. As EEG measures electric potential differences, no absolute values can be given. Rather, all results of qEEG analysis depend on the chosen reference electrode or montage. For some qEEG measures this influence has

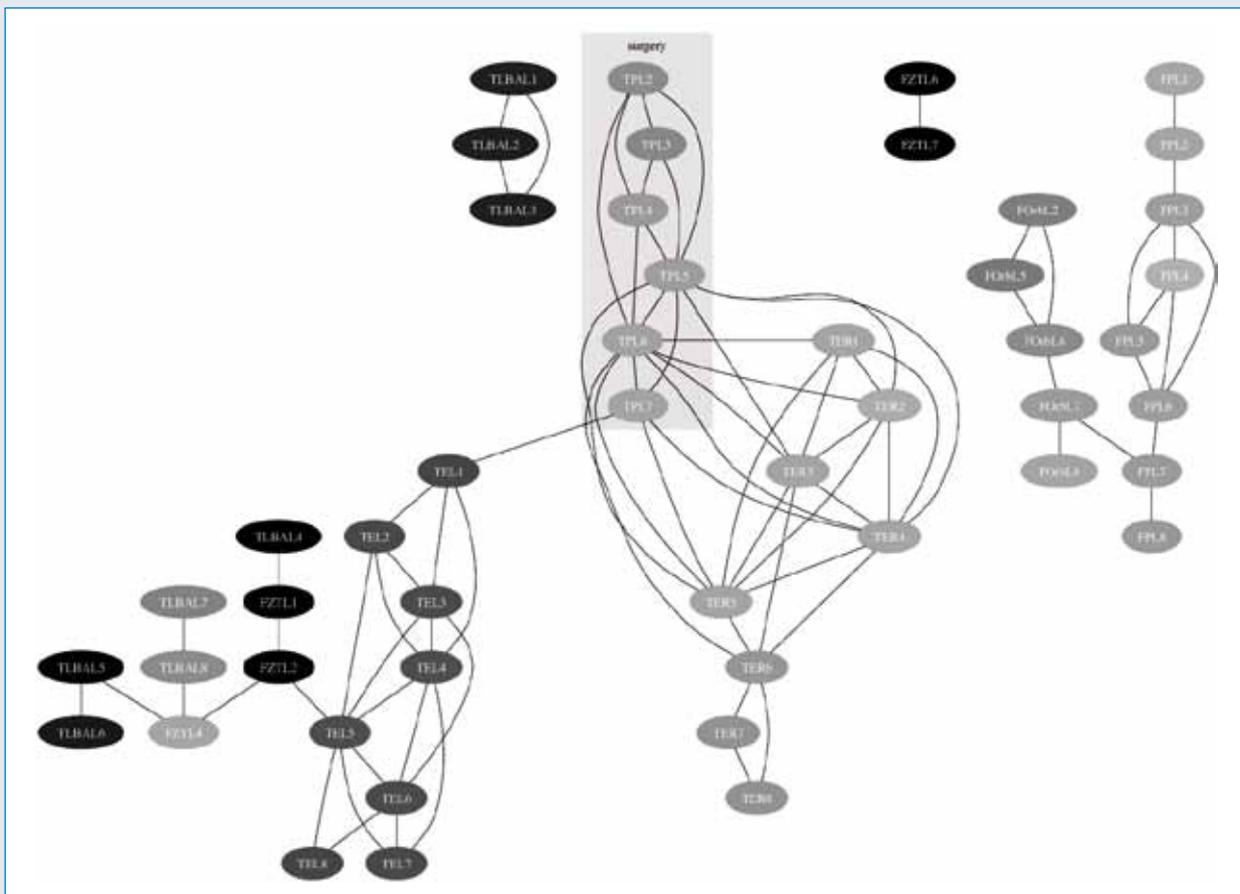


Figure 10: Binary graph visualization of the CCS matrix network of Figure 8b. All channels are represented by a node and all significant matrix elements are drawn as a link, regardless of sign (correlation or anti-correlation) and strength of the interaction. The shading of the nodes informs about the change of local efficiency as compared to the mean of  $N=100$  network randomizations. For the original iEEG all efficiencies are smaller than in random networks with darker colors indicating larger changes. Channels recording from tissue that was later surgically removed in this patient are highlighted in grey.

been studied systematically [63-65]. A general advice for an “optimal” reference is impossible. Rather, references that obviously influence a qEEG measure should be avoided and in case of doubt analysis should be repeated using different montages. Another caveat that is often discussed in regard to EEG interrelation measures is „volume conduction“, i.e. the fact that electric potentials are effective also at distances and in free space. Due to the relatively small size of human brains (diameter <20cm) volume conduction propagates through the whole brain in less than a nanosecond, i.e. instantaneously on time scales measurable by EEG (typical time scale: milliseconds). Therefore, one possibility to suppress spurious interrelation due to this effect is by looking only at finite temporal lags between signals. One has to be aware, however, that besides volume conduction this rather crude filtering may eliminate “true” interactions taking place at zero lag, too. In addition, electric fields may well have physiologic effects, too [66].

Nonlinear time series analysis of neurophysiologic data [22, 24, 25] has long been “en vogue”. Later, the importance of nonlinearity in neurophysiological time series and especially the capability of measures to detect nonlinearities reliably from short and noisy experimental data have been challenged. Comparing the sensitivity and specificity of various bivariate interrelation measures for model data, it was recently found that linear measures perform equally well or even better than nonlinear measures – even if the signals or the interrelation were indeed nonlinear [67-69]. However, there are indications that a separation of significantly nonlinear from entirely linear interrelation may reveal useful additional information. For a collection of univariate and bivariate measures it has been found that correction of nonlinear qEEG measures by surrogates with identical linear properties increases the ability for lateralization of the SOZ [13, 52]. A first multivariate study along similar lines has been carried out in [51], finding indications that localization of SOZ may be supported by searching for brain areas with increased significant nonlinearities.

In the last years application of so-called “micro electrodes” in parallel to normal iEEG electrodes has become possible. These micro electrodes record the discharges of small groups of neurons or even of single units and can be used to study high frequency oscillations, see article by J. Jacobs in this issue. Recently a unified approach to detect directional interrelations between pairs of spike time series, pairs of time continuous signals as well as between pairings of spike time series with time continuous signals was proposed by Andrzejak and Kreuz [70]. This approach promises to be of high value for the study of micro electrode recordings of neuronal spiking and local field potentials. Without doubt it is necessary to further extend such qEEG tools to address the specific characteristics of these signals as well as of the combination of micro

and macro electrodes.

Future developments of qEEG analysis will also include integration with other modalities, such as fMRI (see article by M. Hauf et al. in this issue) or functional near-infrared spectroscopy (fNIRS), both assessing the hemodynamic response of cerebral vessels. fNIRS is a noninvasive technique, whose spatial and temporal resolution is comparable with scalp EEG. In contrast to fMRI interaction with EEG is negligible and head motion is tolerated well. This makes combined EEG-fNIRS a promising tool for investigating of normal and pathological brain function.

Despite the considerable progress that has been achieved in development of qEEG analysis techniques, it certainly has not yet been integrated into clinical routine. In the future, efforts will have to be increased to close the gap between research applications and everyday clinical EEG assessment. Furthermore, it is conceivable – and maybe desirable – that with the help of a variety of qEEG analysis techniques epilepsy surgery of the future will increasingly consist in targeted disconnection of epileptic networks rather than in a complete removal of the SOZ.

## References

1. Lüders HO. *Textbook of Epilepsy Surgery*. London: Informa Healthcare, 2008
2. Elger CE, Schmidt D. *Modern treatment of epilepsy: A practical approach*. *Epilepsy Behav* 2008; 12: 501
3. Rosenow F, Lüders H. *Presurgical evaluation of epilepsy*. *Brain* 2001; 124: 1683
4. Niedermeyer E, Lopes da Silva F. *Electroencephalography, Basic Principles, Clinical Applications and Related Fields*. Baltimore: Williams & Wilkins, 1999
5. Zschocke S. *Klinische Elektroenzephalographie*. Berlin: Springer, 2002
6. Hamer HM, Morris HH, Mascha EJ et al. *Complications of invasive video-EEG monitoring with subdural grid electrodes*. *Neurology* 2002; 58: 97
7. Gotman J. *Automatic detection of seizures and spikes*. *J Clin Neurophysiol* 1999; 16: 130-140
8. Stacey WC, Litt B. *Technology insight: neuroengineering and epilepsy – designing devices for seizure control*. *Nat Clin Pract Neurol* 2008; 4: 190-201
9. Mormann F, Andrzejak RG, Elger CE, Lehnertz K. *Seizure prediction: the long and winding road*. *Brain* 2007; 130: 314
10. Mormann F, Kreuz T, Rieke C et al. *On the predictability of epileptic seizures*. *Clin Neurophys* 2005; 116: 569
11. Andrzejak RG, Chicharro D, Elger CE, Mormann F. *Seizure prediction: Any better than chance?* *Clin Neurophysiol* 2009; 120: 1465-1478
12. Andrzejak RG, Lehnertz K, Rieke C et al. *Indications of nonlinear deterministic and finite dimensional structures in time series of brain electrical activity: Dependence on recording region and brain state*. *Phys Rev E* 2001; 64:061907
13. Andrzejak RG, Mormann F, Widman G et al. *Improved characterization of the epileptic brain by focusing on nonlinearity*. *Epilepsy Res* 2006; 69, 30-44
14. Lehnertz K, Arnhold J, Grassberger P, Elger CE. *Chaos in Brain?* Singapore:

- World Scientific Publishing, 2000
15. Buzsáki G. *Rhythms of the Brain*, New York: Oxford University Press, 2006
  16. Schindler K, Wiest R, Kollar M, Donati F. Using simulated neuronal cell models for detection of epileptic seizures in foramen ovale and scalp EEG. *Clin Neurophysiol* 2001; 112: 1006-1017
  17. Schindler K, Elger CE, Lehnertz K. Increasing synchronization may promote seizure termination: Evidence from status epilepticus. *Clin Neurophysiol* 2007; 118: 1955-1968
  18. Niederhauser JJ, Esteller R, Echazu J et al. Detection of seizure precursors from depth-EEG using a sign periodogram transform. *IEEE Trans Biomed Eng* 2003; 51: 449-458
  19. Gardner A, Worrell G, Marsh E et al. Human and automated detection of high-frequency oscillation in clinical intracranial EEG recordings. *J Clin Neurophysiol* 2007; 118: 1134-1143
  20. Schindler K, Leung H, Lehnertz K, Elger CE. How generalised are secondarily "generalised" tonic-clonic seizures? *J Neurol Neurosurg Psychiatry* 2007; 78: 993-996
  21. Schreiber T. Interdisciplinary application of nonlinear time series methods. *Phys Rep* 1999; 308: 1-64
  22. Kantz H, Schreiber T. *Nonlinear Time Series Analysis*, 2nd edition. Cambridge: Cambridge University Press, 2004
  23. Galka A. *Topics in Nonlinear Time Series Analysis: With Implications for EEG Analysis*. Singapore: World Scientific Publishing, 2000
  24. Stam CJ. Nonlinear dynamical analysis of EEG and MEG: Review of an emerging field. *Clin Neurophysiol* 2005; 116: 2266-2301
  25. Pereda E, Quiroga R, Bhattacharya J. Nonlinear multivariate analysis of neurophysiological signals. *Prog Neurobiol* 2005; 77: 1
  26. Takens F. Detecting strange attractors in turbulence. In: Rand DA, Young LS (eds): *Dynamical Systems and Turbulence, Lecture Notes in Mathematics* 898. Berlin: Springer, 1981
  27. Rapp PE, Bashore TR, Martinerie JM et al. *Brain Topogr* 1989; 2: 99
  28. Martinerie J, Adam C, Le Van Quyen M et al. Epileptic seizures can be anticipated by non-linear analysis. *Nat Med* 1998; 4: 1173-1176
  29. Lehnertz K, Elger CE. Can epileptic seizures be predicted? Evidence from nonlinear time series analysis of brain electrical activity. *Phys Rev Lett* 1998; 80: 5019-5022
  30. Theiler J, Rapp PE. Re-examination of the evidence for low-dimensional, nonlinear structure in the human electroencephalogram. *Electroencephalogr Clin Neurophysiol* 1996; 98: 213-222
  31. Schindler K, Gast H, Stieglitz L et al. Forbidden ordinal patterns of perictal intracranial EEG indicate deterministic dynamics in human epileptic seizures. *Epilepsia* 2011; 52: 1771-1780
  32. Bandt C. Ordinal time series analysis. *Ecol Model* 2005; 182: 229-238
  33. Amigo J, Kocarev L, Szczepanski J. Order patterns and chaos. *Phys Lett* 2006; A355: 27-31
  34. Schreiber T, Schmitz A. Surrogate time series. *Physica D* 2000; 142: 346
  35. Bulmer MG. *Principles of Statistics*. New York: Dover Publications, 1979
  36. Kraskov A, Stögbauer H, Grassberger P. Estimating mutual information. *Phys Rev E* 2004; 69: 066138
  37. Hlavackova-Schindler K, Palus M, Vejmelka M, Bhattacharya J. Causality detection based on information-theoretic approaches in time series analysis. *Phys Rep* 2007; 441: 1-46
  38. Chen YH, Rangarajan G, Feng JF, Ding MZ. *Phys Lett* 2004; A324: 26
  39. Schreiber T. Measuring information transfer. *Phys Rev Lett* 2000; 85: 461-464
  40. Staniak M, Lehnertz K. Symbolic transfer entropy. *Phys Rev Lett* 2008; 100: 158101
  41. Rosenblum MG, Pikovsky AS. Detecting direction of coupling in interacting oscillators. *Phys Rev E* 2001; 64: 045202
  42. Chicharro D, Andrzejak RG. Reliable detection of directional couplings using rank statistics. *Phys Rev E* 2009; 80: 026217
  43. Siegel S, Castellan NJ Jr. *Nonparametric Statistics for the Behavioral Sciences*. New York: McGraw-Hill, 1988
  44. Müller M, Baier G, Galka A et al. Detection and characterization of changes of the correlation structure in multivariate time series. *Phys Rev E* 2005; 71: 046116
  45. Plerou V, Gopikrishnan P, Rosenow B et al. Random matrix approach to cross correlations in financial data. *Phys Rev* 2002; E65: 066126
  46. Schindler K, Leung H, Elger CE, Lehnertz K. Assessing seizure dynamics by analysing the correlation structure of multichannel intracranial EEG. *Brain* 2007; 130: 65-77
  47. Müller M, Baier G, Rummel C, Schindler K. Estimating the strength of genuine and random correlations in non-stationary multivariate time series. *Eur Phys Lett* 2008; 84: 10009
  48. Müller M, Baier G, Rummel C, Schindler K. Evolution of genuine cross-correlation strength of focal seizures. *J Clin Neurophysiol* 2011; 28: 450-462
  49. Kramer MA, Eden UT, Kolaczyk ED et al. Coalescence and fragmentation of cortical networks during focal seizures. *J Neurosci* 2010; 30: 10076-10085
  50. Rummel C, Müller M, Baier G. Analyzing spatio-temporal patterns of genuine cross-correlations. *J Neurosci Meth* 2010; 191: 94-100
  51. Rummel C, Abela E, Müller M et al. Uniform approach to linear and nonlinear interrelation patterns in multivariate time series. *Phys Rev E* 2011; 83: 066215
  52. Andrzejak RG, Chicharro D, Lehnertz K, Mormann F. Using bivariate signal analysis to characterize the epileptic focus: The benefit of surrogates. *Phys Rev* 2011; E83: 046203
  53. Boccaletti S, Latora V, Moreno Y et al. Complex networks: Structure and dynamics. *Phys Rep* 2006; 424: 175-308
  54. Stam CJ, Reijneveld JC. Graph theoretical analysis of complex networks in the brain. *Nonlin Biomed Phys* 2007; 1: 3
  55. Kramer MA, Cash SS. Epilepsy as a Disorder of Cortical Network Organization. *Neuroscientist* 2012; Jan 10, epub ahead of print
  56. Stam CJ, van Straaten ECW. The organization of physiological brain networks. *Clin Neurophysiol* 2012; in press
  57. Kramer MA, Eden UT, Cash SS, Kolaczyk ED. Network inference with confidence from multivariate time series. *Phys Rev E* 2009; 79: 061916
  58. Schindler K, Bialonski S, Hostmann M-T et al. Evolving functional network properties and synchronizability during human epileptic seizures. *Chaos* 2008; 18: 033119
  59. Ponten SC, Douw L, Bartolomei F et al. Indications for network regularization during absence seizures: weighted and unweighted graph theoretical analyses. *Exp Neurol* 2009; 217: 197-204
  60. Horstmann MT, Bialonski S, Noennig N et al. State dependent properties of epileptic brain networks: comparative graph-theoretical analyses of simultaneously recorded EEG and MEG. *Clin Neurophysiol* 2009; 121: 172-185
  61. Kuhnert MT, Elger CE, Lehnertz K. Long-term variability of global statistical properties of epileptic brain networks. *Chaos* 2010; 20: 043126
  62. Wilke C, Worrell G, He B. Graph analysis of epileptogenic networks in human partial epilepsy. *Epilepsia* 2011; 52: 84-93
  63. Schiff SJ. Dangerous phase. *Neuroinformatics* 2005; 3: 315-317
  64. Guevara R, Pérez Velázquez JL, Nenadovic V et al. Phase synchronization measurements using electroencephalographic recordings – What can we

- really say about neuronal synchrony? Neuroinformatics 2005; 3: 301-313*
65. Rummel C, Baier G, Müller M. *The influence of static correlations on multivariate correlation analysis of the EEG. J Neurosci Meth 2007; 166: 138-157*
66. Fröhlich F, McCormick DA. *Endogenous electric fields may guide neocortical network activity. Neuron 2010; 67: 129-143*
67. Ansari-Asl K, Senhadji L, Bellanger J-J, Wendling F. *Quantitative evaluation of linear and nonlinear methods characterizing interdependencies between brain signals. Phys Rev E 2006; 74: 031916*
68. Kreuz T, Mormann F, Andrzejak RG et al. *Measuring synchronization in coupled model systems: A comparison of different approaches. Physica D 2007; 225: 29*
69. Wendling F, Ansari-Asl K, Bartolomei F, Senhadji L. *From EEG signals to brain connectivity: A model-based evaluation of interdependence measures. J Neurosci Meth 2009; 183: 9-18*
70. Andrzejak RG, Kreuz T. *Characterizing unidirectional couplings between point processes and flows. Europhys Lett 2011; 96: 50012*

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### Summary

Intracranial EEG information used for epilepsy surgery has been provided from large widely spaced electrodes over a narrow bandwidth. However, over the last decades, research on animal and more recently on human, promoted by increased interest in developing high-density microelectrode arrays (MEA), has opened new windows for the comprehension of seizure origin and propagation at a submillimeter scale. From an electrophysiological perspective MEA demonstrate to be able to record local field potentials recordings and possibly single units in the mouse cortex. The limitations on the number of channels that can be recorded simultaneously may limit the number of microelectrodes that can be considered and consequently the extent of brain coverage. Thanks to improving microfabrication techniques, several prototypes of MEA are under development and investigation. They will certainly play an important role in the improvement of the understanding of the complicated and evolving concept of epileptogenesis and provide the development of new strategies regarding neurosurgical therapeutic issues.

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**Key words:** EEG, microrecording, epilepsy, surgery, microfabrication, micro-electrode array

### Die Zukunft der intrakraniellen EEG-Ableitung bei Epilepsie: eine Frage der Technologie?

Intrakranielle EEG-Signale wurden bisher mit Elektroden aufgezeichnet, die eine relativ grosse räumliche Distanz zueinander hatten und nur eine stark begrenzte Frequenzbandbreite erfassten. In den letzten Jahren hat aber die Entwicklung von sogenannten Mikro-Elektroden-Arrays (MEA), welche im Tierversuch

und auch bereits beim Menschen zum Einsatz kommen, die Möglichkeit eröffnet, Anfallsentstehung und Anfallsausbreitung auch auf einer Grössenskala <1mm zu analysieren. So wurde zum Beispiel in Mäusen gezeigt, dass mit MEA sowohl die lokalen elektrischen Feldpotenziale als auch Aktionspotenziale einzelner Nervenzellen aufgezeichnet werden können. Die begrenzte Anzahl von Signalen, die gleichzeitig registriert werden können, stellt eine Einschränkung insofern dar, als deshalb aktuell nur ein kleines Hirnareal mit MEA exploriert werden kann. Dank der stetigen Verbesserung der Mikrofabrikationstechnologie werden aber mehrere neue Prototypen von MEA entwickelt und bereits getestet. Diese neuen MEA werden mit Sicherheit in Zukunft eine wichtige Rolle für ein verbessertes Verständnis der Ikto- und Epileptogenese spielen und wesentlich dazu beitragen, neue therapeutische Strategien in der Epilepsiechirurgie zu entwickeln.

**Schlüsselwörter:** EEG, Mikro-Ableitung, Epilepsie, Chirurgie, Mikro-Fabrikation, micro-electrode array

### Le futur de l'enregistrement EEG intracrânien pour l'épilepsie : une question technologique ?

Les informations concernant l'EEG intracrânien utilisées pour la chirurgie d'épilepsie ont été obtenues avec des grandes électrodes largement espacées sur une bande passante étroite. Cependant, au cours des dernières décennies, la recherche sur l'animal et plus récemment sur l'homme, motivée par l'intérêt accru pour le développement de microelectrode arrays (MEA), a ouvert de nouvelles fenêtres concernant la compréhension l'origine et la propagation des crises épileptiques à une échelle sous-millimétrique. D'un point de vue électrophysiologique, les MEA ont montré qu'elles étaient capable d'enregistrer des potentiels de champ proche, voire même des enregistrements monocellulaires dans

le cortex de souris. Le nombre limité de canaux d'enregistrement limite le nombre d'électrode simultanément utilisables et, par conséquent, l'étendue de la surface cérébrale à explorer. Grâce à l'amélioration des techniques de microfabrication, plusieurs prototypes de MEA sont en cours de développement et d'essai. Ils joueront certainement un rôle important dans l'amélioration de la compréhension de ce concept compliqué et en évolution qu'est l'épileptogenèse et permettront de développer de nouvelles stratégies thérapeutiques neurochirurgicales.

**Mots clés :** EEG, micro-enregistrement, épilepsie, chirurgie, microfabrication, micro-electrode array

## Introduction

Partial epilepsy is the most common pharmacologically resistant seizure disorder [1]. Although the established electrophysiological signature of partial epilepsy is focal seizures, little is known about the spatial and temporal scales that define the neuronal assemblies underlying this emergent pathological oscillation. For decades, epilepsy surgery has utilized intracranial EEG recorded over a narrow bandwidth (1–100 Hz) from large (~5–10mm diameter), widely spaced (5–10 mm) electrodes [2]. This practice, however, is largely based upon tradition and the limits of sensor technology when intracranial EEG was first recorded, rather than our knowledge of the human brain. These technological limitations often frustrate epileptologists looking for discrete, functional 'lesions' to remove during epilepsy surgery, because seizures arising from the neocortex often appear to start abruptly from large regions of brain [3]. Other applications awaiting better definition of the neurophysiological generators of seizures are seizure prediction [4, 5], whose controversial performance may be due in part to the poor temporal and spatial resolution of clinical intracranial EEG, and implantable anti-epileptic devices [6], whose efficacy might be improved with better targeting and understanding of seizure generators. To date the emergence of spontaneous focal seizures in humans has not been thoroughly investigated at high temporal sampling rates on sub-millimeter spatial scales.

Over the last few years, there has been increased interest in developing high-density arrays of electrodes or microelectrodes incorporating microwires, placed separately or in conjunction with regular macroelectrode grids or depths. In addition to providing denser sampling of cortical activity, these arrays are better suited to recording high-frequency activity. These new recording electrodes have been used mostly for research purposes without established clinical applications, but reports raise the possibility that such high-density arrays with smaller electrodes can record information important for identifying the ictal onset zone and planning

surgical resections.

## From animal...

Work from Goldensohn et al. [7] in the 1960s describes microepileptiform discharges obtained from a glass pipette electrode on the surface of cat cortex treated with a focal injection of penicillin. They demonstrated focal evolving microepileptiform discharges after penicillin injection on single electrodes in an array of electrodes spaced 2mm apart with no reflection of the discharges on adjacent electrodes. The magnitudes of the recorded potentials were as large as 3mV and were largest in the superficial cortical layers when depth profiles were measured.

More recently, literature about exploration of the content of the EEG in a frequency domain higher than what is permitted by commonly used macroelectrodes emerged. In a rat model of epilepsy created by intra-hippocampal kainic acid injection [8], pathological high-frequency oscillations emerged in microdomains (<1mm<sup>3</sup>) weeks to months before spontaneous seizures developed. Epileptogenesis was proposed to be initiated by local cellular injury, resulting in small clusters of pathologically interconnected neurons. The authors hypothesize that pathologically interconnected neurons generate hypersynchronous discharges that kindle the brain through the creation of new pathological microdomains, and the emergence of an interacting network of pathologically interconnected neuron clusters.

## ... to human data

Wide-bandwidth local field potential recordings using microelectrodes (diameter<100 μm) in epileptic human hippocampus and neocortex have identified several new classes of electrographic activity localized to sub-millimetre-scale tissue volumes, inaccessible to standard clinical intracranial EEG technology. Pathological high-frequency oscillations have been localized to microdomains (<1mm<sup>3</sup>) in human epileptic hippocampus [9, 10]. Penetrating microelectrode arrays embedded directly into human epileptic neocortex reveal microperiodic epileptiform discharges [11] and high-frequency oscillations [12] confined to 200-μm-diameter tissue regions. There is debate regarding the significance of microperiodic epileptiform discharges, however, because they have morphology and temporal behaviour similar to what is reported after cortical injury [13], and they have not been established as a specific electrophysiological marker for epileptic tissue.

Stead et al. [14] recorded microseizures and microdischarges, more frequently in the seizure onset zone but also occurring less frequently in control patients. These recordings assess not single-unit activity, but multineuronal activity. Still these studies report the

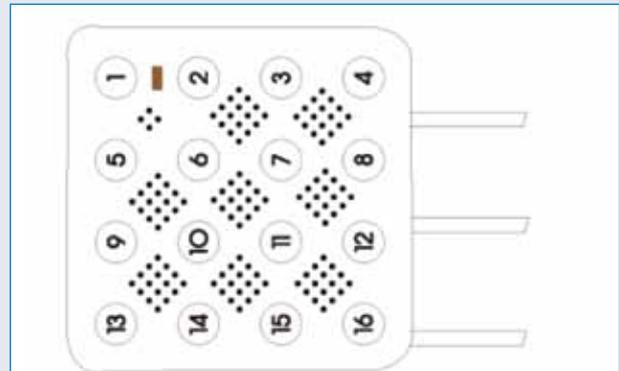
ability of these new electrodes to assess highly localized activity and, in the case of the microseizures reported by Stead and colleagues, activity that may correlate with region of onset of partial seizures. If that would be the case, those microseizures would be ideal candidates for targeted therapies.

### High-density microelectrode arrays

Multiple electrode arrays (microelectrode arrays - MEAs) consist of a substrate on top of which coplanar electrodes are manufactured, concentrating them into a limited area. A first type of MEAs is used for *in-vitro* electrophysiological experiments, aiming at performing multiple parallel measurement of the electrical activity of cell cultures, where the older patch-clamping based technology would typically enable up to six or eight parallel measurements, only. Typically, the electrode pitch is in the range of 200 $\mu\text{m}$  [15] down to 60 $\mu\text{m}$  for recent developments, with 512 individual recording sites [16]. Electrical connectivity is provided to the borders of the system, translating dimensions one to two higher orders of magnitude. MEAs have gained a wide acceptance in the community of neuroscientists, and are a standard tool for *in-vitro* experiments. Currently used MEAs are purely passive devices, which creates the stringent need to place dedicated amplification devices in the closest vicinity. MEAs using three dimensional microelectrode tips have been demonstrated recently. The use of non-invasive electrodes that do not penetrate the cell membrane presents significant challenges. Fromherz [17] has pioneered this field, first presenting gate-less FET transistors to detect extracellular neuronal electrical activity [18], and more recently extending this work to capacitive sensors. A non-standard CMOS process has been applied in the development by Cohen et al. [19] where floating-gate transistors have their gate-voltage potential affected by cells appropriately placed on them. Silicon post-processing of a chip produced in standard CMOS technology has been demonstrated as a reliable technique to fabricate planar electrodes and connect them with readout electronics [20]. The inter-electrode pitch is usually in the order of several tens of micrometers, leaving significant area for local electronic processing and relatively large electrode plates. The highest density array reported to date has an inter-electrode pitch equal to 7.8 $\mu\text{m}$  [21]. Finally, using three-dimensional micromachined microelectrodes to couple to living matter has been attempted [22] where electrodes are 40 $\mu\text{m}$  high, only 15 $\mu\text{m}$  being exposed, and with a minimal pitch of 170 $\mu\text{m}$ , and [23] where electrodes are >50 $\mu\text{m}$  high, one of the 60 available electrode covering an area of 60 $\mu\text{m}$  x 60 $\mu\text{m}$ .

An example of current solution for high-density recording of epileptic activity on the human cortical surface consist of hybrid macroelectrodes along with microwire arrays with bundles of wires connected to

the electrodes (AD-Tech, Inc.). The microwire arrays contain 40- $\mu\text{m}$ -diameter platinum-iridium wire spaced 0.5-1 mm apart. Macrocontacts are 4-mm-diameter platinum-iridium discs spaced 5-10 mm apart, center-to-center (**Figure 1**).

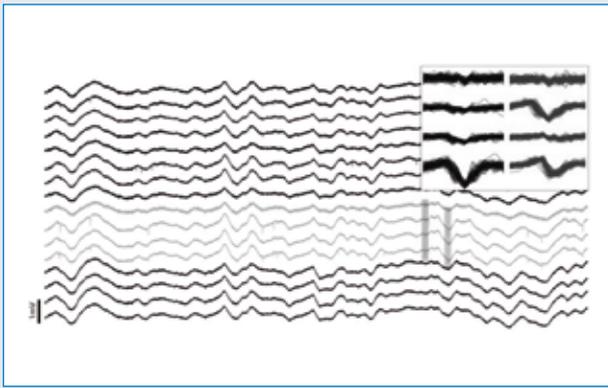


**Figure 1:** Scheme of a hybrid electrode macroelectrodes along with microwire arrays with bundles of wires connected to the electrodes proposed by AD Tech.

### Signals recorded from MEA

From an electrophysiological perspective, the extracellular local field potentials recorded by microwires seem to be primarily a manifestation of the co-operative activity of the local neuronal population. Until recently, the local field potential was thought to exclusively reflect the summation of post-synaptic currents because of their relatively slow dynamics. This is the reason that extracellularly recorded action potentials – with the fast  $\text{Na}^+$  current being the largest contributor – are detected only if the microwire is close to the cell. The amplitude of the extracellular action potential falls off rapidly with distance, and the events are unlikely to constructively sum because of their brief duration. However, it has been recognized that there are additional sources of local field potentials not associated with synaptic currents and they can be significant [24]. They include  $\text{Ca}^{++}$ -mediated action potentials generated in dendrites [25], slow long-lasting calcium-mediated potassium currents, voltage-dependent intrinsic oscillations in neurons [26] and currents related to glia-neuron interactions [27].

Recently, we performed acute *in-vivo* recordings in mice with a novel, flexible, polyimide neural probe with two layers of platinum electrodes [28]. The devices were packaged ensuring robustness and biocompatibility. Using electrical modeling and impedance testing the device has shown to be adequate for neural recording experiments. Single and multiple units were identified. Principal Component Analysis is used to quantify the quality of the recordings. **Figure 2** demonstrates local field recordings identifying two single units in the

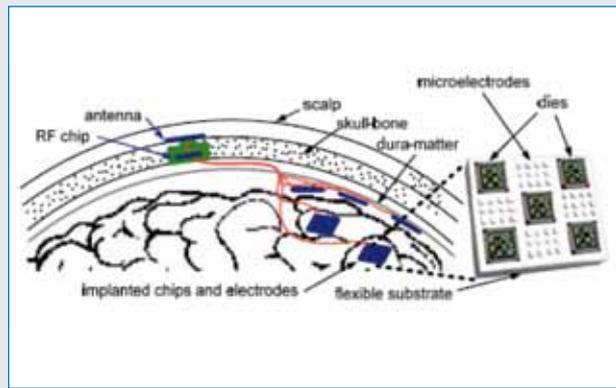


**Figure 2:** Recordings from of a 16 MEA polyimide neural probe with two layers of platinum electrodes on mouse cortex, Adapted from Mercanzini A et al. *Sensors and Actuators A*, 2008.

mouse cortex. All 16 electrode sites were active. Histological study of the limited tissue reaction around the implant showed the long term implant stability [29].

### Extent of coverage

The extent of coverage by recording arrays is in part dependent on the knowledge of the localization of the ictal onset zone. The ictal onset zone may be much more localized than the epileptogenic zone (the region targeted for resection for optimal surgical outcome) or the irritative zone (corresponding to interictal discharges), but even experts acknowledge that these zones are often overlapping and often not clearly defined [30]. For the purposes of early seizure detection, one would want to be as close as possible to the ictal onset zone. In some patients this is a discrete region; in other patients (e.g., patient with nonlesional neocortical partial epilepsy), the ictal onset zone may be broad or regional. Although it is not uncommon to incorporate 100-200 intracranial contacts into macroelectrode recording arrays, there are some limits on the size and extent of the arrays posed by the extent of the craniotomy and inherent risks of larger arrays. The use of high-density electroencephalography employing larger arrays of electrodes for scalp recordings is oriented toward dipole source localization. These larger arrays have been shown to provide improvements in effective spatial resolution up to 512 electrodes if the noise level remains low [31]. In intracranial recording, the incorporation of microelectrode arrays placed within the space of traditional grid arrays offers an increased density of points of measure which can provide a superior understanding of the local network dynamic involved in the early stages of the seizure [14]. Still, the limitations on the number of channels that can be recorded simultaneously may limit the number of microelectrodes that can be considered. The use of macroelectrodes may remain a valid compromise between size of the electrodes and



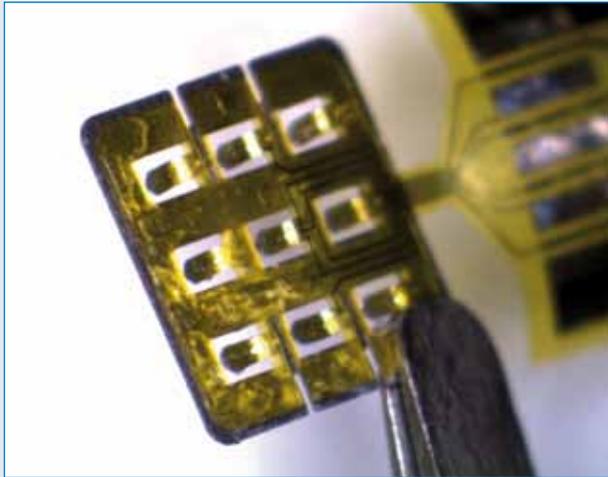
**Figure 3:** Schematic representation of the proposed Wireless MEA.

area of the brain covered, especially in the context of the presurgical evaluation where the location of the seizure focus is not yet clearly identified. Thereafter, the use of MEA could be used for a further refinement of the ictal/epileptogenic zone.

### Ongoing developments

Another solution consisting of using highly flexible and thin substrates to create active electrode arrays combining a large number of electrodes with integrated circuits distributed over a relatively large area over the cortex is under development in partnership with engineers of the Swiss Federal School of Technology. By placing many of these recording systems on the potentially epileptic parts of the cortex previously detected by the standard non-invasive methods, sufficient information with respect to the localization of the epileptic foci with high spatial resolution quality could be recorded (**Figure 3**). Low-noise amplifiers that operate in an intermediate range of frequency to record low as well as high frequency ripple and/or spiking signals which can be representatives of epilepsy are integrated in the system. Furthermore, subcutaneous implantation is enabled by the presence of an RF chipset located in a burr hole in the skull for remote powering and wireless data transmission (**Figure 3**), avoiding the risk of infection induced by the externalized wires. Finally, long-term recordings could be performed, providing refined information from each patient. Implantation of this device should be performed through a minimally invasive approach and transmission of the patient data could even be performed on an outpatient basis. Verification of the proof of concept of this technology is under investigation on animal.

Future MEA designs for human use could also incorporate several microelectrode elements disposed on an implantable slightly penetrating device, in order to record deeper cortical neuronal layers. **Figure 4**



**Figure 4:** Early prototype of a MEA which is intended to sit on the surface of the brain, with slightly penetrating shanks wearing microelectrodes.

demonstrates an early prototype of the cortSTIM (Aleva Neurotherapeutics SA, Lausanne) which is intended to sit on the surface of the brain, with slightly penetrating shanks and on which microelectrode recordings are disposed. This design offers a truly 3D volume from which to capture single unit and local field potential recordings with higher signal-to-noise ratios than classic EEG electrodes. Furthermore, the 3D nature of the electrode layout offers also novel possibilities in cortical stimulation.

## Conclusions

Recent technological developments improving microfabrication techniques have provided new insights in seizure detection at a submillimetric scale. Increasing evidence that microseizures may precede detectable epileptic events at a standard electrocorticographic scale opens new frontiers not only for the comprehension of seizure origin and propagation, but also regarding neurosurgical therapeutic issues (increasing selectivity of tissue resection, earlier seizure detection and targeted suppression by electrical stimulation before clinical manifestation). In other words, each step of the detection paradigm can be a target of future experiments to bring to fruition a seizure warning mechanism that can significantly improve the quality of life of patients or to optimize closed loop therapy devices. From the choice of electrodes to the decision making algorithm, it is important to take a comprehensive look at the various elements that are part of this complicated and evolving process.

## References

- Engel J, Wiebe S, French J et al. Practice parameter: temporal lobe and localized neocortical resections for epilepsy: report of the Quality Standards Subcommittee of the American Academy of Neurology, in association with the American Epilepsy Society and the American Association of Neurological Surgeons. *Neurology* 2003; 60: 538-547
- Engel J, Pedley TA, Aicardi J et al. *Epilepsy: a Comprehensive Textbook*. Philadelphia PA: Lippincott Williams & Wilkins, 2007
- Quesney LF. Intracranial EEG investigation in neocortical epilepsy. *Adv Neurol* 2000; 84: 253-274
- Lehnertz K, Litt B. The first international Collaborative Workshop on seizure prediction: summary and data description. *Clin Neurophysiol* 2005; 116: 493-505
- Mormann F, Andrzejak RG, Elger CE, Lehnertz K. Seizure prediction: the long and winding road. *Brain* 2007; 130: 314-333
- Sun FT, Morrell MJ, Wharen RE. Responsive cortical stimulation for the treatment of epilepsy. *Neurotherapeutics* 2008; 5: 68-74
- Goldensohn ES. Initiation and propagation of epileptogenic foci. In: JK Penry and DD Daly (eds): *Advances in Neurology*. New York: Raven Press, 1975
- Bragin A, Wilson CL, Engel JJ. Chronic epileptogenesis requires development of a network of pathologically interconnected neuron clusters: a hypothesis. *Epilepsia* 2000; 41(Suppl 6): S144-S152
- Bragin A, Wilson CL, Staba RJ et al. Interictal high-frequency oscillations (80-500 Hz) in the human epileptic brain: entorhinal cortex. *Ann Neurol* 2002; 52: 407-415
- Worrell GA, Gardner AB, Stead SM et al. High-frequency oscillations in human temporal lobe: simultaneous microwire and clinical macroelectrode recordings. *Brain* 2008; 131: 928-937
- Schevon CA, Ng SK, Cappell J et al. Microphysiology of epileptiform activity in human neocortex. *J Clin Neurophysiol* 2008; 25: 321-330
- Schevon CA, Trevelyan AJ, Schroeder CE et al. Spatial characterization of interictal high frequency oscillations in epileptic neocortex. *Brain* 2009; 132: 3047-3059
- Ebersole JS, Pedley TA. *Current Practice of Clinical Electroencephalography*. Philadelphia: Lippincott Williams & Wilkins, 2003
- Stead M, Bower M, Brinkmann BH et al. Microseizures and the spatio-temporal scales of human partial epilepsy. *Brain* 2010; 133: 2789-2797
- Jimbo Y, Kasai N, Torimitsu K et al. A System for MEA-based multisite stimulation. *IEEE Trans Biomed Eng* 2003; 50: 241-248
- Mathieson K, Kachiguine S, Adams C et al. Large-Area microelectrode arrays for recording of neural signals. *IEEE Trans Nucl Sci* 2004; 51: 2027-2031
- Fromherz P. *The Neuron-Semiconductor Interface*. Willner I, Katz E (eds): *Bioelectronics*. Weinheim: Wiley-VCH, 2005; Ch.12: 339-394
- Vassanelli S, Fromherz P. Transistor records of excitable neurons from rat brain. *Appl Phys A* 1998; 66: 459-463
- Cohen A, Spira ME, Ytshaik S et al. Depletion type floating p-channel MOS transistor for recording action potentials generated by cultured neurons. *Biosens Bioelectron* 2004; 19: 1703-1709
- Heer F, Hafizovic S, Franks W et al., CMOS microelectrode array for bidirectional interaction with neuronal networks. *IEEE JSSC* 2006; 41: 1620-1629
- Lambacher A, Jenkner M, Merz M et al. Electrical imaging of neuronal activity by multi-transistor-array (MTA) recording at 7.8µm resolution. *Appl Phys A* 2004; 79: 1607-1611
- Isik S, Berdondini L, Oni J et al. Cell-compatible array of three-dimensio-

- nal tip electrodes for the detection of nitric oxide release. *Biosens Bioelectron* 2005; 20: 1566-1572
23. Nam Y, Wheeler BC, Heuschkel MO. Neural recording and stimulation of dissociated hippocampal cultures using microfabricated three-dimensional tip electrode array. *J Neurosci Methods* 2006; 155: 296-299
24. Buzsaki G, Traub RD, Pedley TA. The cellular basis of EEG activity. In: Ebersole JS, Pedley TA (eds): *Current Practice of Clinical Electroencephalography*. Philadelphia: Lippincott Williams & Wilkins, 2003
25. Wong RK, Prince DA, Basbaum AI. Intradendritic recordings from hippocampal neurons. *Proc Natl Acad Sci USA* 1979; 76: 986-990
26. Leung LW, Yim CY. Intrinsic membrane potential oscillations in hippocampal neurons in vitro. *Brain Res* 1991; 553: 261-274
27. Tian GF, Azmi H, Takano T et al. An astrocytic basis of epilepsy. *Nat Med* 2005; 11: 973-981
28. Mercanzini A, Cheung K, Buhl DL et al. Demonstration of cortical recording using novel flexible polymer neural probes. *Sensors and Actuators A: Physical* 2008; 143: 90-96
29. Mercanzini A, Colin P, Bensadoun JC et al. In vivo electrical impedance spectroscopy of tissue reaction to microelectrode arrays. *IEEE Trans Biomed Eng* 2009; 56: 1909-1918
30. Worrell GA. Sensing the body electric: biomarkers of epileptic brain. *Epilepsy Curr* 2011; 11: 118-119
31. Ryyanen OR, Hyttinen JA, Malmivuo JA. Effect of measurement noise and electrode density on the spatial resolution of cortical potential distribution with different resistivity values for the skull. *IEEE Trans Biomed Eng* 2006; 53: 1851-1858

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## Alfred-Hauptmann-Preis

Dieser Preis ist nach dem deutschen Neurologen und Psychiater Alfred Hauptmann (1881 - 1948) benannt. Er hatte u.a. schon 1912 – noch als Assistenzarzt – erstmals auf die antiepileptische Wirkung von Phenobarbital aufmerksam gemacht. 1935 wurde er aufgrund seiner jüdischen Abstammung von den Nationalsozialisten aus dem Dienst als Direktor der Psychiatrischen und Nervenklinik der Universität Halle/Saale entfernt und musste in die USA emigrieren.

Der Preis wurde von 1980 bis 2008 in der Regel alle zwei Jahre durch das Epilepsie-Kuratorium e.V. vergeben, ab 2009 ist es ein gemeinsamer Preis der Deutschen Gesellschaft für Epileptologie, der Österreichischen Sektion der Internationalen Liga gegen Epilepsie und der Schweizerischen Liga gegen Epilepsie mit Vergabe auf den alle zwei Jahre stattfindenden gemeinsamen Tagungen.

Ausgezeichnet wird die beste wissenschaftliche Arbeit aus dem deutschsprachigen Raum auf dem Gebiet der experimentellen und klinischen Epileptologie aus den beiden letzten, der Verleihung vorangegangenen Jahren.

Arbeiten werden besonders aus den Fachgebieten Neurologie, Pädiatrie, Psychiatrie, klinische Pharmakologie, Neurophysiologie und Neurobiologie erwartet.

Die ausgezeichneten Personen erhalten eine Urkunde. Darüber hinaus ist der Preis mit

**10'000 Euro**

dotiert. Das Preisgeld wird ab 2009 von der Firma UCB GmbH (Deutschland), Monheim, zur Verfügung gestellt. Es können mehrere Einzelpersonen oder Arbeitsgruppen ausgezeichnet werden.

Die Arbeiten sollten in englischer Sprache verfasst sein. Zusätzlich zu den Arbeiten sind folgende weitere Unterlagen einzureichen:

- ein Lebenslauf,
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- für den Fall von Mehrautorenarbeiten, bei denen nicht alle Autoren am Preis beteiligt werden sollen, eine Aussage über den Anteil der einzelnen Autoren an der publizierten Arbeit.

Die Arbeiten sind in vierfacher Ausführung bis zum

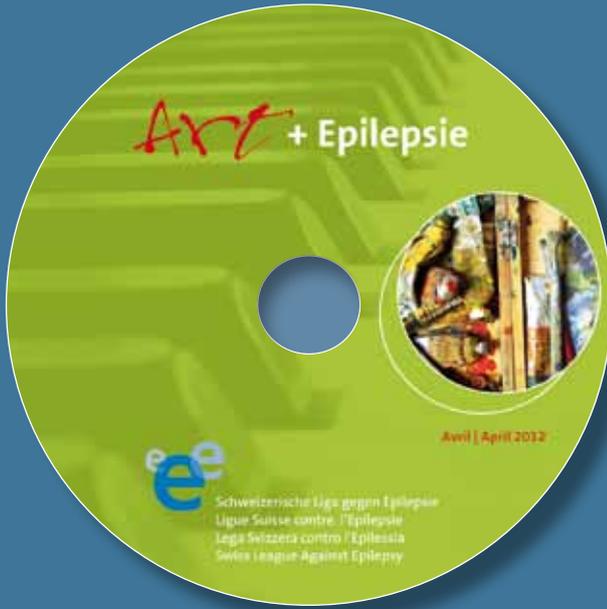
**31.12.2012**

an den Vorsitzenden des Kollegiums zu senden:

**Herrn Dr. med. Günter Krämer  
Medizinischer Direktor  
Schweizerisches Epilepsie-Zentrum  
Bleulerstrasse 60  
CH 8008 Zürich**

Es können sowohl unveröffentlichte als auch publizierte Arbeiten eingereicht werden. Bei der Einreichung ist mitzuteilen, ob und wo die Arbeit zum ersten Mal veröffentlicht wurde. Die Arbeiten sollen in deutscher oder englischer Sprache verfasst sein. Dem Kollegium können auch Arbeiten zur Preisvergabe vorgeschlagen werden.

Preisrichterkollegium: Dr. med. Günter Krämer (Vorsitzender), Schweizerisches Epilepsie-Zentrum Zürich, Prof. Dr. med. Rudolf Korinthenberg, Universitätskinderklinik Freiburg, Prof. Dr. med. Wolfgang Löscher, Institut für Pharmakologie, Toxikologie und Pharmazie, Hannover, Günther Sperk, Univ.-Prof. Dr. Abteilung Pharmakologie, Medizinische Universität, Innsbruck.



PD Dr. med. Fabienne Picard, Epilepsie-Liga-Mitglied, hatte zum Ziel, mit einer DVD über Kunst und Epilepsie Menschen anzusprechen, welche sich vor dieser Krankheit fürchten, sie unheimlich finden und am liebsten nichts darüber wissen möchten. Sie verpackt Informationen mit Kunstgenuss, die Epilepsie-Liga freut sich über das Angebot, diese DVD in ihre Reihe aufnehmen zu dürfen.

Die DVD wurde in französischer Sprache produziert, begleitet von einem Booklet auf Deutsch und auf Französisch.

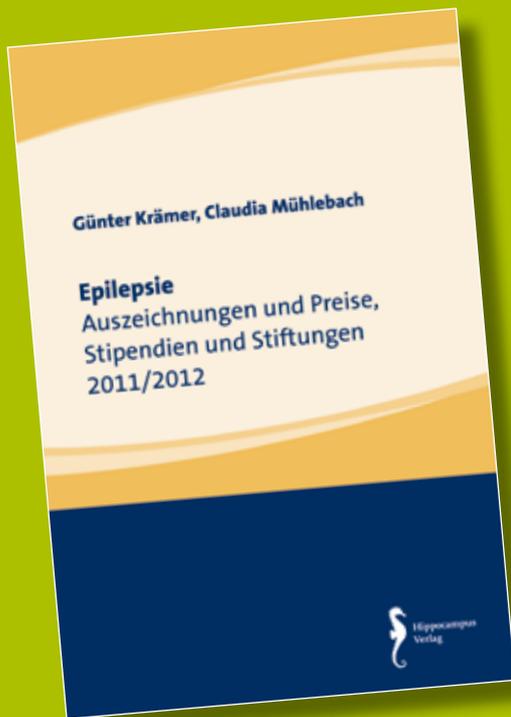
PD Dr méd. Fabienne Picard, membre de la Ligue contre l'Épilepsie, voulait créer un DVD associant art et épilepsie dans le but de s'adresser aux personnes à qui cette maladie fait peur, qu'elle inquiète et qui, en conséquence, préféreraient ne pas en entendre parler. Elle réussit à faire passer l'information à travers le plaisir que procure l'art et la Ligue contre l'Épilepsie se réjouit de pouvoir accueillir son DVD parmi ses publications.

Le DVD a été produit en langue française avec des sous-titres en allemand. Il est accompagné d'un livret en allemand et en français.



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info@epi.ch**

### Vorschau Epileptologie 3 | 2012

**Einführung und Kommentar zur Neuauflage der Dissertation von Louis Florentin Calmeil „DE L'ÉPILEPSIE“ von 1824  
Faksimile der Dissertation**



### Ausschreibung – Promotionspreis

**Die Schweizerische Liga gegen Epilepsie (Epilepsie-Liga) vergibt alle 3 Jahre einen Preis in Höhe von**

**CHF 10'000.—**

**für die beste Dissertation auf dem Gebiet der Epileptologie.**

Bewerbungen sind aus allen Fachbereichen und Berufsgruppen möglich und erwünscht, sowohl aus Grundlagen- als auch klinischen Fächern. Eine Altersbeschränkung erfolgt nicht.

Das Preisrichterkollegium setzt sich aus drei Vorstandsmitgliedern der Epilepsie-Liga zusammen, das bei Bedarf zusätzlich externe Gutachter hinzuziehen kann. Es trifft seine Entscheidung in geheimer Wahl.

Falls der Antragsteller/die Antragstellerin bereits anderswo Anträge für Unterstützung gestellt hat, ist offen zu legen, bei wem und mit welchem Ergebnis.

Die Preisverleihung erfolgt jeweils im darauf folgenden Jahr anlässlich der Jahrestagung oder Mitgliederversammlung der Epilepsie-Liga.

Bewerbungen sind **bis zum 31.12.2012** an die **Geschäftsstelle der Epilepsie-Liga** (Seefeldstrasse 84, Postfach 1084, 8034 Zürich) einzureichen und müssen beinhalten: vier Exemplare der abgeschlossenen und beim Dekanat eingereichten Dissertation, vier Exemplare einer Stellungnahme des Doktorvaters (dabei kann es sich auch um das entsprechende Gutachten für die Dissertation handeln).

## Forschungsprojekt ausgezeichnet

Der diesjährige Forschungsförderungspreis der Epilepsie-Liga geht an Professor Bernhard Schmitt von der Universitätskinderklinik, Abteilung für Klinische Neurophysiologie/Epilepsie, Zentrum für Schlafmedizin, Zürich. Sein Forscherteam befasst sich mit dem Einfluss von Hypsarrhythmie und Spike Waves auf den Slow Wave-Schlaf bei Kindern mit Blitz-Nick-Salaam(BNS)-Epilepsie und Auswirkungen auf die kognitive Entwicklung im Alter von 18 Monaten.



In einer ersten Studie konnte gezeigt werden, dass die physiologischen Veränderungen der Slow Waves bei Kindern mit ESES (electrical status epilepticus in slow wave sleep) gestört sind. Es fand sich im Nachtschlaf von ESES-Kindern kein Abfall der Slow Wave-Steigung und die Abnahme der Slow Wave-Amplitude war signifikant kleiner als in der gleichaltrigen Kontrollgruppe. Dies impliziert, dass Funktionen der Slow Waves oder die synaptische Homeostase bei ESES möglicherweise beeinträchtigt sind und dies die Entwicklungsschritte der Kinder erklären könnte.

Es liegt nahe, dass der Enzephalopathie bei Kindern mit BNS-Epilepsie ähnliche Mechanismen zu Grunde liegen wie bei den Kindern mit ESES. Mit dem vorgeschlagenen Projekt sollen die Zusammenhänge zwischen Spike Waves bei Kindern mit BNS und dem Verhalten der Slow Waves während des Nachtschlafs untersucht und die elektrophysiologischen Prozesse mit den höheren Hirnfunktionen in Verbindung gebracht werden.

Fragestellung 1 untersucht den quantitativen Zusammenhang zwischen dem Abfall von Amplitude und Slope der Slow Waves und dem Spike Wave-Index (SWI). Gemäss der Hypothese des Forscherteams sind die Auswirkungen auf die Abnahme von Amplitude und Steigung der Slow Waves im NREM-Schlaf umso ausge-

prägter, je höher der Spike Wave-Index (SWI) ist.

Fragestellung 2 untersucht den Zusammenhang zwischen Spike Wave-Index und deren Auswirkung auf Amplitude und Steigung der Slow Waves einerseits und dem kognitiven Entwicklungsstand mit 18 Monaten andererseits. Hier wird ein stärkerer Entwicklungsrückstand erwartet, wenn der SWI hoch und die Abnahme von Steigung und Amplitude der Slow Wave niedrig ist.

## Projet de recherche récompensé

**Cette année, le Prix de soutien de la recherche de la Ligue Suisse contre l'Epilepsie a été décerné au Professeur Bernhard Schmitt, du service de neurophysiologie clinique/épilepsie (centre de médecine du sommeil) de la clinique pédiatrique universitaire de Zurich. Son équipe de chercheurs étudie l'influence de l'hypsarythmie et des pointes-ondes sur le sommeil à ondes lentes chez les enfants atteints d'épilepsie de West et ses conséquences sur leur développement cognitif à l'âge de 18 mois.**

Une première étude a permis de montrer que les modifications physiologiques des ondes lentes sont perturbées chez les enfants souffrant d'ESES (état de mal épileptique électrique pendant le sommeil lent). Pendant le sommeil nocturne des enfants atteints d'ESES, il n'y a pas eu de baisse de la pente des ondes lentes et la diminution de l'amplitude des ondes lentes était significativement inférieure à celle observée chez le groupe témoin de même âge. Cela implique que les fonctions des ondes lentes ou l'homéostasie synaptique pourraient être perturbées dans l'ESES et serait susceptible d'expliquer les retards de développement des enfants.

Une hypothèse plausible est que l'encéphalopathie des enfants atteints d'épilepsie de West repose sur les mêmes mécanismes que celle des enfants atteints d'ESES. Le projet soumis se propose d'étudier les liens entre les pointes-ondes chez les enfants ayant des crises cloniques et le comportement des ondes lentes pendant le sommeil nocturne et d'établir la relation entre les processus électrophysiologiques et les fonctions cérébrales supérieures.

La première question porte sur le lien quantitatif entre la diminution de l'amplitude et de la pente des ondes lentes et l'index de pointes-ondes (SWI). Selon l'hypothèse de l'équipe de chercheurs, les effets de la baisse de l'amplitude et de la pente des ondes lentes dans le sommeil non-REM sont d'autant plus marqués que l'index de pointes-ondes (SWI) est élevé.

La deuxième question consiste à examiner le lien entre l'index de pointes-ondes et son impact sur l'amplitude et l'inclinaison des ondes lentes d'une part et avec l'état de développement cognitif à 18 mois d'autre part. Ici, l'on s'attend à un retard de développement plus important lorsque le SWI est élevé et que la baisse de la pente et de l'amplitude des ondes lentes est faible.



### Führungswechsel an der Klinik Bethesda

**Der Vorstand des Fürsorgevereins Klinik Bethesda Tschugg hat Herrn Dr. med. Klaus Meyer per 1. Juni 2012 zum Chefarzt und Medizinischen Direktor ernannt. Er tritt die Nachfolge des aus gesundheitlichen Gründen zurückgetretenen Dr. med. Fabio Baronti an, welcher während 10 Jahren die Klinik führte.**

Dr. Meyer ist seit 1993 als Kaderarzt, seit 2002 als Chefarzt-Stellvertreter, in der Klinik Bethesda tätig. Der in Bayreuth gebürtige und seit 20 Jahren in der Schweiz wohnhafte Arzt bildete sich in Erlangen, Ulm, Bayreuth und Pfäfers fort. Die 1992 und 1993 erworbenen Facharztstitel für Neurologie und Psychiatrie sind Ecksteine auf seinem Lebensweg, wobei die Neurologie schon immer sein Schwerpunktgebiet darstellte. Er erwarb in der Folge die schweizerischen Zertifikate für Elektroenzephalographie (EEG), Klinische Neurophysiologie, Elektroneuromyographie (ENMG) und Zerebrovaskuläre Krankheiten. Als Facharzt für Neurologie FMH mit psychiatrischer Ausbildung überzeugt er durch eine ganzheitliche Sicht- und Behandlungsweise der Epilepsie, was insbesondere auch die Klinik Bethesda auszeichnet, die aufgrund ihrer Vernetzung und der intensiven, auch internen Kollaboration der drei Bereiche Neurorehabilitation, Bewegungsstörungen und Epilepsie in der Schweiz und in den benachbarten Ländern einzigartig ist. Die Epileptologie der Klinik Bethesda ist im Rahmen eines Epilepsienetzwerkes u.a. eng mit den Universitätsspitalern Bern und Basel verbunden. Seit Beginn seiner Tätigkeit in Tschugg ist Dr. Meyer massgeblich am Aufbau der Klinikstruktur beteiligt und dementsprechend mit dem Unternehmen bestens vertraut.

Dr. Meyer ist ein national anerkannter Spezialist im Fachgebiet der Epileptologie. Durch seine langjährige Funktion als stellvertretender Chefarzt der Klinik und Leiter des Epilepsiebereiches ist er Vorstandsmitglied in mehreren nationalen und regionalen Fachgesellschaften – u.a. in der Schweizerischen Liga gegen Epilepsie und im ärztlichen Bezirksverein Seeland (AeBS). Er ist bestens vernetzt, wirkt zudem in Ausbildungs-

kommissionen mit und publiziert regelmässig in Fachzeitschriften.

Unter der Führung von Dr. Meyer wird die Klinik Bethesda weiterhin Gewähr bieten für Zuverlässigkeit und Kontinuität sowie die stetige Weiterentwicklung des medizinischen Angebots.

### Changement de direction à la clinique Bethesda

**Le conseil d'administration du Fürsorgeverein Klinik Bethesda à Tschugg a nommé le Dr méd. Klaus Meyer médecin responsable et directeur médical à effet du 1er juin 2012. Il succède au Dr méd. Fabio Baronti qui a dirigé la clinique pendant 10 ans et s'est retiré pour raisons médicales.**

Le Dr Meyer travaille à la Clinique Bethesda depuis 1993 en tant que médecin cadre, et depuis 2002 comme adjoint du médecin responsable. Né à Bayreuth et domicilié en Suisse depuis plus de 20 ans, il a suivi ses études à Erlangen, Ulm, Bayreuth et Pfäfers. Ses titres de spécialiste en neurologie et en psychiatrie, obtenus en 1992 et 1993, constituent les pierres angulaires de son curriculum, quoique la neurologie ait toujours été son domaine de prédilection. Il a ensuite obtenu les certificats suisses de formation en électroencéphalographie (EEG), en neurophysiologie clinique, en électroneuromyographie (ENMG) et en maladies cérébrovasculaires. En tant que spécialiste en neurologie FMH doté d'une formation en psychiatrie, il convainc par sa vision et son traitement globaux de l'épilepsie, qui caractérise notamment aussi la clinique Bethesda. Celle-ci occupe une position unique en Suisse et dans les pays voisins du fait de l'interconnexion et de la collaboration intensive, y compris au niveau interne, entre les trois domaines de la neuro-rééducation, des troubles moteurs et de l'épilepsie. Le service d'épileptologie de la clinique Bethesda est entre autres étroitement lié aux hôpitaux universitaires de Berne et de Bâle dans le cadre d'un réseau Epilepsie. Depuis son entrée en fonction à Tschugg, le Dr Meyer s'est fortement impliqué dans l'édification de la structure de la clinique et est par conséquent parfaitement familiarisé avec l'entreprise.

Le Dr Meyer est un spécialiste en épileptologie reconnu au niveau national. Ayant été longtemps l'adjoint du médecin responsable de la clinique et le directeur du secteur épilepsie, il fait partie du conseil d'administration de plusieurs sociétés spécialisées régionales et nationales, parmi lesquelles la Ligue Suisse contre l'Epilepsie et le cercle médical Seeland. Il possède un excellent réseau relationnel, participe par ailleurs à des commissions de formation et est régulièrement publié dans des revues spécialisées.

Sous la direction du Dr Meyer, la clinique Bethesda continuera d'assurer fiabilité et constance, ainsi que de garantir le développement permanent de l'offre médicale.

### Mise au concours – Soutien de la recherche

Promotion de la recherche scientifique dans le domaine de l'épilepsie (surtout sous forme d'aide initiale) par la Ligue Suisse contre l'Epilepsie (Ligue contre l'Epilepsie)

La Ligue contre l'Epilepsie soutient les projets scientifiques dans le domaine de l'épileptologie par un montant total de

**CHF 20'000.—**

par an, la priorité étant accordée aux projets cherchant à élucider les causes et à mettre au point des traitements de l'épilepsie.

Aucune bourse ne sera octroyée pour la formation de base ou continue ou pour des séjours à l'étranger. En revanche, la prise en charge de frais de voyage et de séjour (sans salaire) est possible pour les séjours de courte durée (quelques semaines au maximum) lorsque ces séjours servent à apprendre des méthodes appliquées dans le cadre d'un projet bénéficiant de soutien en Suisse.

Si le requérant a déjà fait une demande de soutien ailleurs, il faut nous en informer en spécifiant où et avec quel résultat.

Délai de remise des demandes :

**31 décembre 2012**

Les formulaires, ainsi que le guide pour les candidats peuvent être demandés à l'adresse suivante :

Ligue Suisse contre l'Epilepsie  
Seefeldstrasse 84  
Case postale 1084  
8034 Zurich  
Tél. 043 488 67 77  
Fax 043 488 67 78  
info@epi.ch

### Mise au concours – Prix de promotion

La Ligue Suisse contre l'Epilepsie (Ligue contre l'Epilepsie) décerne tous les 3 ans un prix d'un montant de

**CHF 10'000.—**

pour la meilleure dissertation dans le domaine de l'épileptologie.

Tous les domaines spécialisés et tous les groupes professionnels couvrant les disciplines fondamentales ou cliniques sont invités à soumettre leur candidature. Aucune limite d'âge n'a été fixée.

Le jury décernant le prix se compose de trois membres du comité directeur de la Ligue contre l'Epilepsie. Il peut être complété au besoin par des experts externes. La décision est prise par vote secret.

Si le requérant a déjà fait une demande de soutien ailleurs, il faut nous en informer en spécifiant où et avec quel résultat.

Le prix est toujours décerné l'année suivante dans le cadre de l'assemblée annuelle ou générale de la Ligue contre l'Epilepsie.

Les dossiers de candidature doivent parvenir au Secrétariat de la Ligue contre l'Epilepsie (Seefeldstrasse 84, case postale 1084, 8034 Zurich) jusqu'au

**31.12.2012**

et comporter les pièces suivantes :

- quatre exemplaires de la dissertation achevée et remise au décanat,
- quatre exemplaires d'une prise de position du directeur de thèse (il peut par exemple s'agir de l'expertise concernant la dissertation).

# FIRST ANNOUNCEMENT



## 8. Dreiländertagung 2013

Gemeinsame Jahrestagung  
der Deutschen und Österreichischen Gesellschaften für  
Epileptologie und der Schweizerischen Liga gegen Epilepsie

Gast: Arbeitsgemeinschaft für prächirurgische Diagnostik und operative  
Epilepsitherapie

08.-11. Mai 2013

Congress Centre Kursaal Interlaken, Schweiz  
[www.imk.ch/epilepsie2013](http://www.imk.ch/epilepsie2013)

Deadline Abstract-Einreichung  
15. Januar 2013

### 2012

**8.-13.7.2012** | Rostock, Deutschland  
**The 6th Baltic Sea Summer School on Epilepsy**  
Information: Petra Novotny,  
Prof. Peter & Jytte Wolf Foundation for Epilepsy,  
e-mail: [petra.novotny@wolfstiftung.org](mailto:petra.novotny@wolfstiftung.org),  
[www.epilepsiestiftung-wolf.de/7.html](http://www.epilepsiestiftung-wolf.de/7.html)

**14.-18.7.2012** | Barcelona, Spanien  
**8th FENS Forum of Neuroscience 2012**  
Information: Rachel Bresinger, FENS Forum 2012,  
Kenes International, 1-3 Rue de Chantepoulet,  
CH-1211 Genf 1  
Tel. 0041 / 22 / 9080488 oder 966,  
Fax 0041 / 22 / 9069140,  
e-mail: [rbresinger@kenes.com](mailto:rbresinger@kenes.com)

**14.-25.7.2012** | San Servolo, Venedig, Italien  
**10th International Course on Epilepsy: Management of Seizures and Epilepsies among Neonates and Infants**  
Information: Metella Paterlini,  
Fax: 0039 / 02 / 700445211,  
e-mail: [epilepsysummercourse@univiu.org](mailto:epilepsysummercourse@univiu.org)

**2.-4.8.2012** | St. Paul, MN, USA  
**Annual Convention of the American Society of Electrodiagnostic Technologists - ASET**  
Information: American Society of  
Electroneurodiagnostic Technologists Executive Office,  
6501 East Commerce Avenue, Suite 120, USA Kansas  
City, MO 64120, USA,  
Tel. 001 / 816 / 9311120,  
Fax 001 / 816 / 9311145,  
e-mail: [info@aset.org](mailto:info@aset.org), [www.aset.org](http://www.aset.org)

**16.8.2012** | Basel, 14.15 h  
**Fachveranstaltung der Schweiz. Liga gegen Epilepsie**  
Information: Geschäftsstelle Epilepsie-Liga,  
Seefeldstrasse 84, Postfach 1084, 8034 Zürich  
Tel. 0041 / 43 / 488 67 77,  
Fax 0041 / 43 / 488 67 78,  
e-mail: [info@epi.ch](mailto:info@epi.ch), [www.epi.ch](http://www.epi.ch)

**16.8.2012** | Basel, 18.30 h  
**Publikumsveranstaltung der Schweiz. Liga gegen Epilepsie**  
Information: Geschäftsstelle Epilepsie-Liga,  
Seefeldstrasse 84, Postfach 1084, 8034 Zürich  
Tel. 0041 / 43 / 488 67 77  
Fax 0041 / 43 / 488 67 78  
e-mail: [info@epi.ch](mailto:info@epi.ch), [www.epi.ch](http://www.epi.ch)

**4.-8.9.2012** | Paris, Frankreich  
**21st Congress of the European Sleep Research Society**  
Information: Congrex Switzerland Ltd.,  
Peter Merian-Strasse 80, 4002 Basel,  
Tel. 0041 / 61 / 6867777,  
Fax 0041 / 61 / 6867788,  
e-mail: [basel@congrex.com](mailto:basel@congrex.com),  
[www.congrex.com](http://www.congrex.com),  
[www.congrex.ch/esrs2012](http://www.congrex.ch/esrs2012)

**8.-11.9.2012** | Stockholm, Schweden  
**16th Congress of the European Federation of Neurological Societies (EFNS)**  
Information: Kenes International,  
17 Rue du Cendrier, PO Box 1726, 1211 Geneva 1,  
Tel. 0041 / 22 / 9080488,  
Fax 0041 / 22 / 7322850,  
e-mail: [efns2012@kenes.com](mailto:efns2012@kenes.com),  
[www.kenes.com/efns2012](http://www.kenes.com/efns2012) oder  
[www.efns.org/efns2012](http://www.efns.org/efns2012)

**9.-12.9.2012** | Gargnano/Gardasee, Italien  
**24. Praxisseminar über Epileptologie**  
Information: Stiftung Michael, Münzkamp 5,  
22339 Hamburg, Deutschland,  
Tel.: 0049 / 40 / 5388540,  
Fax: 0049 / 40 / 5381559,  
e-mail: [stiftungmichael@t-online.de](mailto:stiftungmichael@t-online.de)  
[www.seminargargnano.de](http://www.seminargargnano.de)

**15.9.2012** | Zürich  
**Herbstsymposium**  
Information : Schweiz. Epilepsie-Zentrum,  
Bleulerstrasse 60, 8008 Zürich,  
Tel. 0041 / 44 / 387 63 02  
Fax 0041 / 44 / 387 63 96  
e-mail : [leonie.mueller@swissepipi.ch](mailto:leonie.mueller@swissepipi.ch)

20.-22.9.2012 | Marburg, Deutschland

**27. Jahrestagung der Gesellschaft für Neuropsychologie GNP**

Information: GNP-Geschäftsstelle,  
Postfach 11 05, 36001 Fulda, Nikolausstraße 10,  
36037 Fulda, Deutschland,  
Tel.0049 / 700 / 46746700 oder  
0049 / 661 / 9019665,  
Fax 0049 / 661 / 9019692,  
e-mail: fulda@gnp.de,  
www.gnp.de/veranstaltungen/veranstaltungskalender/index.php

26.-29.9.2012 | Hamburg, Deutschland

**Jahrestagung der Deutschen Gesellschaft für Neurologie (DGN) 2012**

Information: Congrex Deutschland GmbH,  
Joachimstaler Str. 12, 10719 Berlin, Deutschland,  
Tel. 0049 / 30 / 8871085550,  
e-mail: dgn@congrex.com, www.congrex.de,  
www.dgn.org

27.-29.9.2012 | Görlitz, Deutschland

**22. Jahrestagung der Deutschen Gesellschaft für Geschichte der Nervenheilkunde – DGGN**

Information: Dr. med. Stephan Jaster, Oberarzt,  
Städtisches Klinikum Dessau, Klinik für Neurochirurgie,  
Auenweg 38, 06847 Dessau-Rosslau, Deutschland,  
Tel. 0049 / 340 / 5011812,  
Fax 0049 / 340 / 5011810,  
e-mail: stephan.jaster@klinikum-dessau.de,  
www.dggn.de

30.9.-4.10.2012 | London, England

**10th European Congress on Epileptology**

Information: ILAE / IBE Congress Secretariat,  
7 Priory Hall, Dublin 18, Ireland,  
Tel. 00353 / 1 / 2056720,  
Fax 00353 / 1 / 2056156.  
Registration Fax 00353 / 1 / 2123576,  
e-mail: london@epilepsycongress.org,  
www.epilepsylondon2012.org

4.10.2012 | St. Gallen

**Tag der Epilepsie**

Information: Geschäftsstelle Epilepsie-Liga,  
Seefeldstrasse 84, Postfach 1084, 8034 Zürich  
Tel. 0041 43 488 67 77  
Fax 0041 43 488 67 78  
e-mail: info@epi.ch, www.epi.ch

7.-9.10.2012 | Boston, USA

**137th Annual Meeting of the American Neurology Association (ANA)**

American Neurological Association, 5841 Cedar Lake  
Road, Suite 204, Minneapolis, MN 55416,  
Tel. 001 / 952 / 5456284,  
Fax 001 / 952 / 5456073,  
e-mail: ana@llmsi.com, www.aneuroa.org

13.-17.10.2012 | New Orleans, Louisiana, USA

**42th Annual Meeting 2012 of the Society for Neuroscience**

Information: Society for Neuroscience, 1121 14th  
Street, NW Suite 1010, Washington, DC 20005, USA,  
Tel. 001 / 202 / 9624000,  
Fax 001 / 202 / 9624941,  
e-mail: info@sfn.org, www.sfn.org

18.10.2012 | Lugano, 14.00 h

**Manifestazione specialistica della Lega Svizzera contro l'Epilessia**

Information: Geschäftsstelle Epilepsie-Liga,  
Seefeldstrasse 84, Postfach 1084, 8034 Zürich  
Tel. 0041 / 43 / 488 67 77  
Fax 0041 / 43 / 488 67 78  
e-mail: info@epi.ch, www.epi.ch

18.10.2012 | Lugano, 18.00 h

**Manifestazione pubblica della Lega Svizzera contro l'Epilessia**

Information: Geschäftsstelle Epilepsie-Liga,  
Seefeldstrasse 84, Postfach 1084, 8034 Zürich  
Tel. 0041 / 43 / 488 67 77  
Fax 0041 / 43 / 488 67 78  
e-mail: info@epi.ch, www.epi.ch

2.-3.11.2012 | Bern

**Joint Annual Meeting. Swiss Society of Neuroradiology (SSNR) and Swiss Society of Neuropediatrics (SSNP)**

Information: IMK Institut für Medizin und  
Kommunikation AG, Münsterberg 1, 4001 Basel,  
Tel. 0041 / 61 / 2713551,  
Fax 0041 / 61 / 2713338,  
e-mail: mail@imk.ch, www.imk.ch/ssnr2012

3.11.2012 | Zürich

**Patiententag**

Information: Geschäftsstelle Epilepsie-Liga,  
Seefeldstrasse 84, Postfach 1084, 8034 Zürich  
Tel. 0041 / 43 / 488 67 77  
Fax 0041 / 43 / 488 67 78  
e-mail: info@epi.ch, www.epi.ch

8.-10.11.2012 | Basel

**188. Jahrestagung der Schweizerischen Neurologischen Gesellschaft (SNG) zusammen mit der Schweizerischen Gesellschaft für Biologische Psychiatrie (SGBP), Gast: Schweizerische Gesellschaft für Verhaltensneurologie (SGVN)**

Information: IMK Institut für Medizin und Kommunikation AG, Münsterberg 1, 4001 Basel,  
Tel. 0041 / 61 / 2713551,  
Fax 0041 / 61 / 2713338,  
e-mail: mail@imk.ch, www.imk.ch/sng188

8.-10.11.2012 | Nizza, Frankreich

**2nd International Congress on Neurology & Epidemiology**

Information : GL events / Package Organisation,  
10 quai Charles de Gaulle, 69463 Lyon Cedex 06,  
Frankreich,  
Tel. 0033 / 4 / 78 76176,  
Fax 0033 / 4 / 78 176 257,  
e-mail: elma.zerzaihi@gl-events.com

14.-17.11.2012 | Quito, Ecuador

**7th Latin American Congress on Epilepsy (LACE)**

Information: ILAE/IBE Congress Secretariat, 7 Priory Hall, Dublin 18, Ireland,  
Tel. 00353 / 1 / 2056720,  
Fax 00353 / 1 / 2056156,  
e-mail: ibedublin@eircom.net,  
www.epilepsycongress.org

22.-24.11.2012 | Interlaken

**188. Tagung der Schweizerischen Neurologischen Gesellschaft (SNG)**

Information: IMK Institut für Medizin und Kommunikation AG, Münsterberg 1, 4001 Basel,  
Tel. 0041 / 61 / 2713551,  
Fax 0041 / 61 / 2713338,  
e-mail: mail@imk.ch

30.11.-4.12.2012 | San Diego, USA

**66th Annual Meeting of the American Epilepsy Society**

Information: American Epilepsy Society (AES), 342 North Main Street, West Hartford, CT 06117-2507 USA,  
Tel. 001 / 860 / 5867505,  
Fax 001 / 860 / 5867550,  
www.aesnet.org

2013

8.-11.5.2013 | Interlaken

**8. Dreiländertagung der Deutschen und Österreichischen Gesellschaften für Epilepsie und der Schweizerischen Liga gegen Epilepsie**

Information: Geschäftsstelle Epilepsie-Liga,  
Seefeldstrasse 84, Postfach 1084, 8034 Zürich,  
Tel. 0041 / 43 / 4886777,  
Fax 0041 / 43 / 4886778,  
e-mail: info@epi.ch  
http://www.epi.ch/

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