

Martinus Hauf<sup>1,2</sup>, Christian Weisstanner<sup>1</sup> and Roland Wiest<sup>1</sup>

<sup>1</sup> University Institute of Diagnostic and Interventional Neuroradiology, Inselspital, University of Bern

<sup>2</sup> Epilepsy Clinic, Clinic Bethesda Tschugg

### Summary

Neuroimaging is one of the main pillars of diagnostic workup in epilepsy. After a first seizure neuroimaging is indicated in all patients but those presenting with a typical genetic generalized epilepsy. Emergency imaging is warranted if the seizures may be the symptom of an acute brain pathology. If the patient returns “back to baseline” at the time of clinical examination, MR imaging may be performed electively using a dedicated epilepsy protocol. Data on seizure recurrence rates over 10 years are still lacking for many classical brain pathologies associated with epilepsy. Novel imaging techniques may be helpful in detecting prolonged seizures and mimics in the emergency setting.

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**Key words:** Epilepsy, guidelines, neuroradiology

### Zerebrale Bildgebung nach einem ersten Anfall

Die zerebrale Bildgebung ist ein zentrales Element der diagnostischen Beurteilung von Epilepsien. Nach einem ersten Anfall ist eine zerebrale Bildgebung bei allen Patienten indiziert, ausser bei Patienten mit einem typischen Bild einer genetisch generalisierten Epilepsie. Eine notfallmässige Bildgebung ist dann notwendig, wenn der Anfall Zeichen einer zugrundeliegenden akuten Hirnerkrankung sein kann. Bei Patienten, die zur Zeit der Untersuchung bereits wieder ihren Normalzustand erreicht haben, kann die MR-Bildgebung elektiv und nach einem speziellen Epilepsieprotokoll durchgeführt werden. Daten zur Wahrscheinlichkeit eines Anfallsrezidivs innerhalb von 10 Jahren, wie in der aktuellen Definition der Epilepsie gefordert, liegen für viele Gehirnpathologien, die mit Epilepsie einhergehen, nicht vor. Neue bildgebende Techniken können hilfreich sein, insbesondere, um in Notfallsituationen prolongierte Anfälle und Epilepsie-Mimikern zu erfassen.

**Schlüsselwörter:** Bildgebung, erster epileptischer Anfall, Epilepsie, Leitlinien

### L'imagerie cérébrale après une première crise

L'imagerie cérébrale représente un important pilier du processus diagnostique en cas d'épilepsie. Après la première crise épileptique une imagerie cérébrale est indiquée chez tous les patients sauf en cas d'épilepsie génétique typique. Une imagerie cérébrale en urgence est nécessaire si la crise peut être signe d'une affection cérébrale aiguë sous-jacente. Si le patient est à nouveau dans son « état habituel » lors de la consultation, une imagerie résonance magnétique peut être effectuée électivement de préférence selon un protocole d'épilepsie spécialisé. Données sur la fréquence de récurrence de crises épileptiques sur 10 ans, comme revendiqué pour la nouvelle définition d'épilepsie, ne sont pas disponibles pour une grande partie de pathologies cérébrales associées à l'épilepsie. Des techniques d'imagerie cérébrale nouvelles peuvent être utilisées notamment en cas d'urgence pour détecter des crises épileptiques prolongées et des mimiqueurs.

**Mots clés :** Imagerie cérébrale, crise épileptique, épilepsie

### Introduction

Neuroimaging constitutes one of the three main pillars in the diagnosis of epilepsy following a first seizure. MR imaging as well as computed tomography allow to screen for pathological conditions and alterations of brain anatomy that promote the development of epilepsy after a first seizure [1]. Epilepsy is characterized as a disorder substantiated by an “enduring predisposition to generate epileptic seizures”. While this condition is fulfilled after two unprovoked seizures (i.e.: i) of unknown etiology or ii) in relation to a demonstrated preexisting brain lesion or progressive CNS disorder), the International League Against Epilepsy (ILAE) has

integrated risk profiles that allow the diagnosis of epilepsy after a first seizure, given an equal risk of > 60% to develop epilepsy (a second unprovoked seizure) within the next 10 years or by the established diagnosis of an epilepsy syndrome [2]. These profiles encompass clinical, neurophysiological and neuroimaging features that predispose to epilepsy [3]:

- i. a prior brain insult; increased relative rate for seizure recurrence at 1 to 5 years 2.55 (95% confidence interval [CI] 1.44 - 4.51)
- ii. an EEG with epileptiform abnormalities; increased relative rate for seizure recurrence at 1 to 5 years of 2.16 (95% CI 1.07 - 4.38)
- iii. a nocturnal seizure; increased relative rate for seizure recurrence at 1 to 4 years of 2.1 (95% CI 1.0 - 4.3)
- iv. abnormal brain imaging; increased relative rate for seizure recurrence at 1 to 4 years of 2.44 (95% CI 1.09 - 5.44)

There is converging evidence from class II and class III studies that “abnormal brain imaging” related to a prior ischemic brain insult, previous brain infection or head trauma equal the risk of a 2nd seizure to predispose to epilepsy [4 - 6]. However, data on the 10 years’ risk of seizure recurrence are lacking for other brain lesions, as e. g. long term epilepsy associated tumors (as e. g. ganglioglioma and dysembryoblastic neuroepithelial tumors or hippocampal sclerosis) [1]. From a health economics point of view, consequences arise since a plain CT in those patients to confirm a remote brain lesion by identifying damage associated with one of the above mentioned lesions would be enough to diagnose epilepsy, however at the risk to overlook other structural lesions that may necessitate intervention.

This short review aims to extend the discussion beyond this current state of evidence towards decision making in clinical practice, where particularly the following questions have to be addressed with priority:

- a. Is the underlying imaging finding of the patient related to a seizure or a mimicking condition (i.e. a seizure like episode)?
- b. Does the underlying imaging finding confirm an underlying acute neurological disorder that has to be immediately treated (i.e. may point towards a symptomatic or provoked seizure)?
- c. Is there a substantial lesion of the brain that explains the first seizure and influences the prognosis – or is it just a coincidental finding?
- d. Are newer imaging techniques available which are promising to increase the diagnostic yield?

For discussion we refer to the guidelines of the German Society of Neurology (DGN) 2012 [7], the British National Institute for Health and Care Excellence (NICE) guidelines [8] and to the American Academy of Neurology (AAN) guidelines on imaging (2015) [3].

#### **a. Is it a seizure or a seizure-like episode?**

Here, two different scenarios must be taken into account. First, under given emergency conditions, without clear confirmation of a witnessed seizure, the principal role of neuroimaging is to rule out potential other causes of persisting neurological deficits not related to a seizure. This may be related to an ischemic stroke with persisting motor deficits and/or aphasia, migraine with aura, a stroke-like episode related to an acute infection (e. g. brain abscess), mitochondrial encephalopathies, malignancies, venous thrombosis or hemorrhage [1, 3]. These conditions may also initially present with a symptomatic (i. e. a provoked) seizure, and special consideration must be given to the precise nosological definition of the underlying condition.

Under such conditions, neuroimaging should be performed immediately in the emergency setting to initiate appropriate treatment as soon as achievable. Computed tomography including contrast administration or – if available – MR imaging should be timely requested. Considering the high numbers of stroke mimickers and chameleons of up to 14% of cases presenting in the ER with stroke-like episodes, appropriate diagnosis may avoid persisting damage due to misinterpretation [9]. Thus, a clear cut clinical description of the condition, the reporting of persisting deficits and the suspected diagnosis is mandatory to guide the neuroradiologist in selecting the appropriate imaging technique [10, 11].

Secondly, patients presenting with a seizure that may be of non-epileptic origin as e. g. syncope, conversion disorders or otherwise not explained mental impairment, and having returned to their baseline clinical status can be scheduled for elective further evaluation that is mainly based on patients history, clinical examination, interictal EEG findings, laboratory results (i. e. creatine kinase evaluation, potentially serum prolactin level changes) and testing of the cardiovascular regulation. For the mimicker, neuroimaging plays a minor role in the etiological workup, yet should be taken into consideration if a vascular or metabolic brain disorder is suspected.

#### **b. Is the seizure a symptom of an underlying acute neurological disorder that has to be further investigated without delay?**

Urgent brain imaging is mandatory after a first seizure, as a seizure may be the first symptom of an acute underlying neurologic disease. It is particularly important in patients who present with a history of a recent head trauma, focal seizure onset, lateralized symptoms on clinical examinations or focal EEG changes [1]. Further consideration should be given to prevalent systemic disorders that may affect the brain, as HIV infection, immunocompromised, anticoagulation, alcoholism or

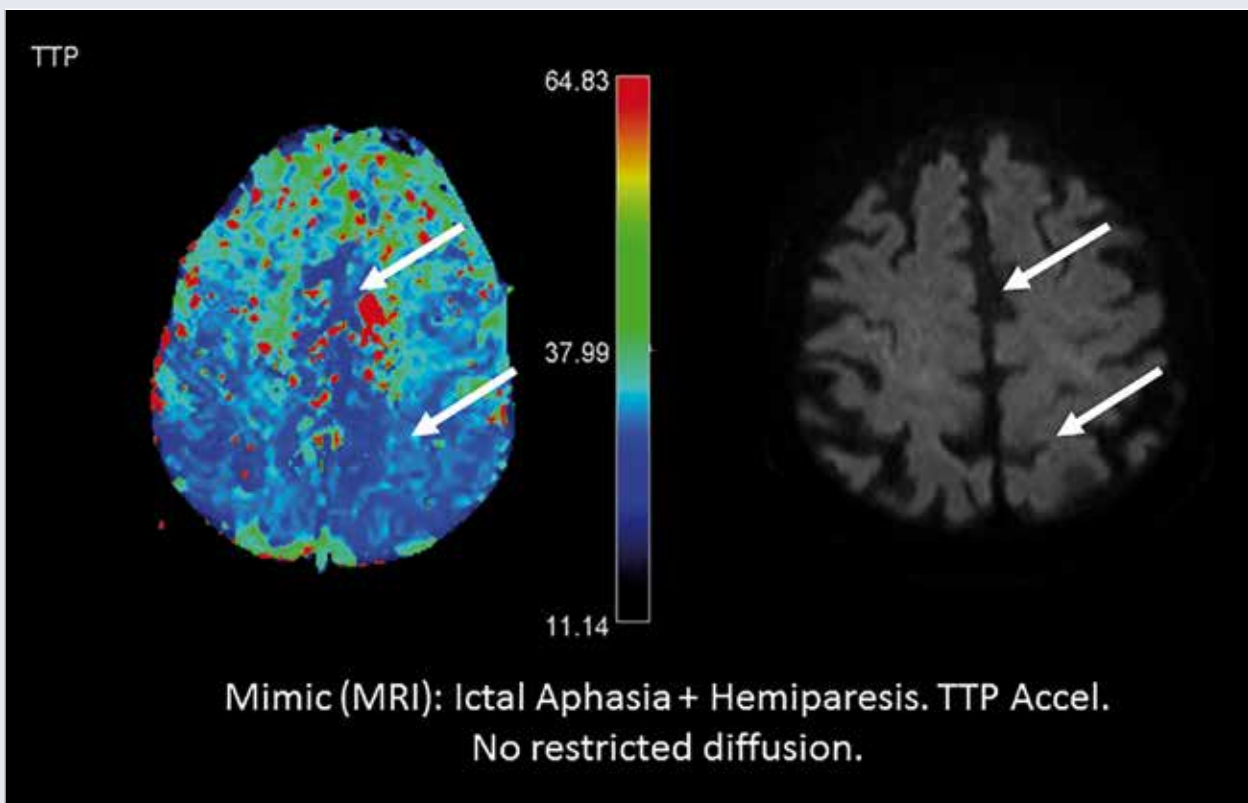
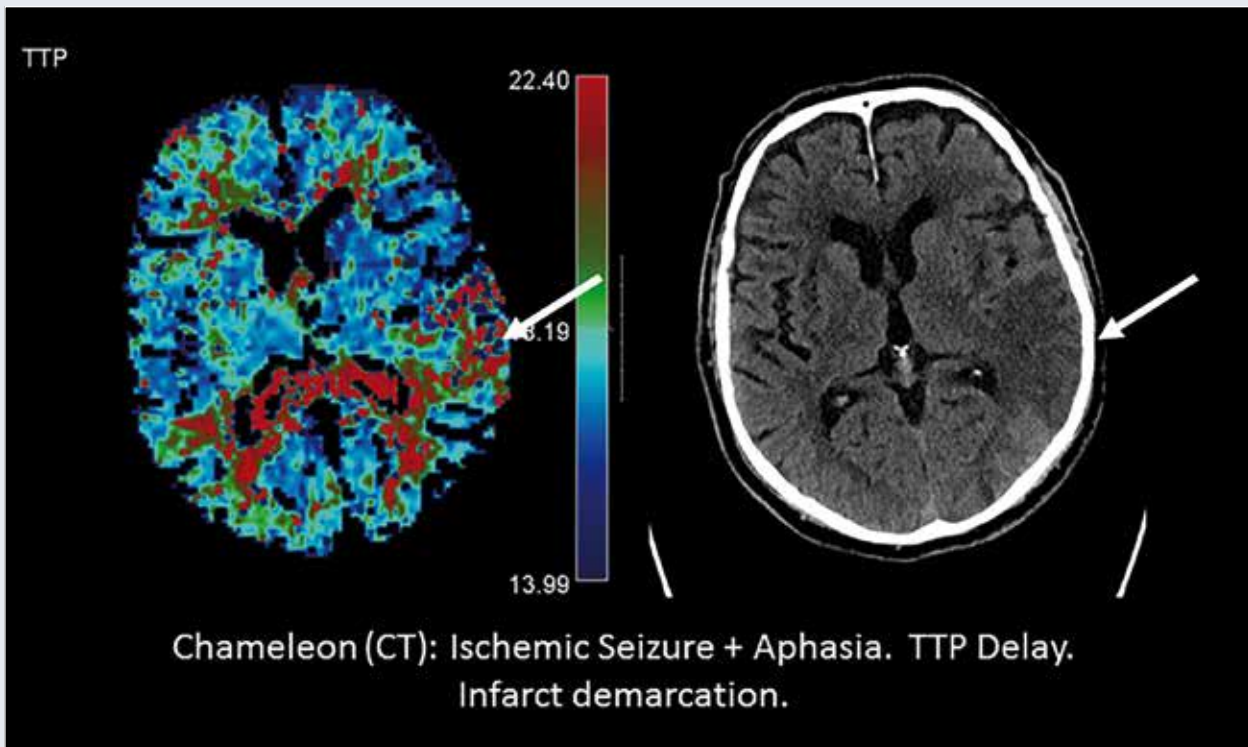


Figure 1 a and 1 b: Stroke presenting with a seizure – Seizure presenting with hemiparesis and aphasia

bleeding diathesis. If there is no direct relationship to an CNS insult, brain imaging may be carried out electively and should directly encompass a dedicated MR epilepsy imaging protocol, as recently proposed by Wellmer and colleagues, preferably using MRI at higher field strengths (3 T) instead of standard protocols [12].

The detection rate of abnormalities detected with neuroimaging lies – dependent on inclusion criteria – between 1 and 48% of all MRI and CT, with recent study of Hakami and coworkers reporting 28% of potentially structural epileptogenic lesions in patients having had an unprovoked epileptic seizure and 53% if the seizures

had a focal onset [13]. While encephalomalacia due to stroke, encephalitis and head trauma is the most frequent abnormality detected in series that included remote symptomatic seizures, it must be emphasized that more than 50% of pathologies others than stroke, hemorrhage, calcifications, encephalomalacia and brain tumors may be obscured by plain CT [14]. Clinically important examples of pathological imaging findings are resumed in Figures 2 - 4.

**c. Is there a substantial lesion of the brain that explains the first seizure and influences the prognosis – or is just a coincidental finding?**

There is evidence from 2 class II and one class III studies that structural brain lesions may generate an enduring predisposition for unprovoked seizures [3]. However, the evidence for the prediction of  $\geq 60\%$  probability of seizure recurrence in 10 years – accord-

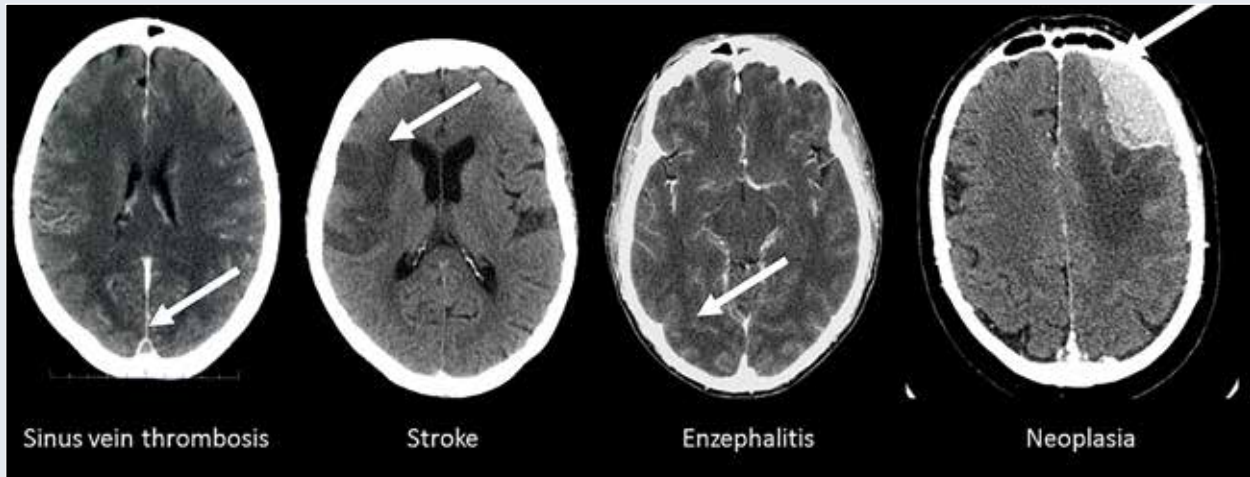


Figure 2: Causes of acute symptomatic seizure, Left: Contrast-enhanced CT-image depicting a thrombus within the superior sagittal sinus. 2nd image left: Acute stroke in the media territory of the right side visualised by hypodense demarcation of parenchyma on unenhanced CT. 3rd image left: Contrast enhanced CT with extravasation of contrast agent in the subarachnoidal space as correlate of blood-brain-barrier dysfunction in meningoencephalitis. Right: Right frontal contrast-enhancing extraaxial tumor suggesting meningioma.

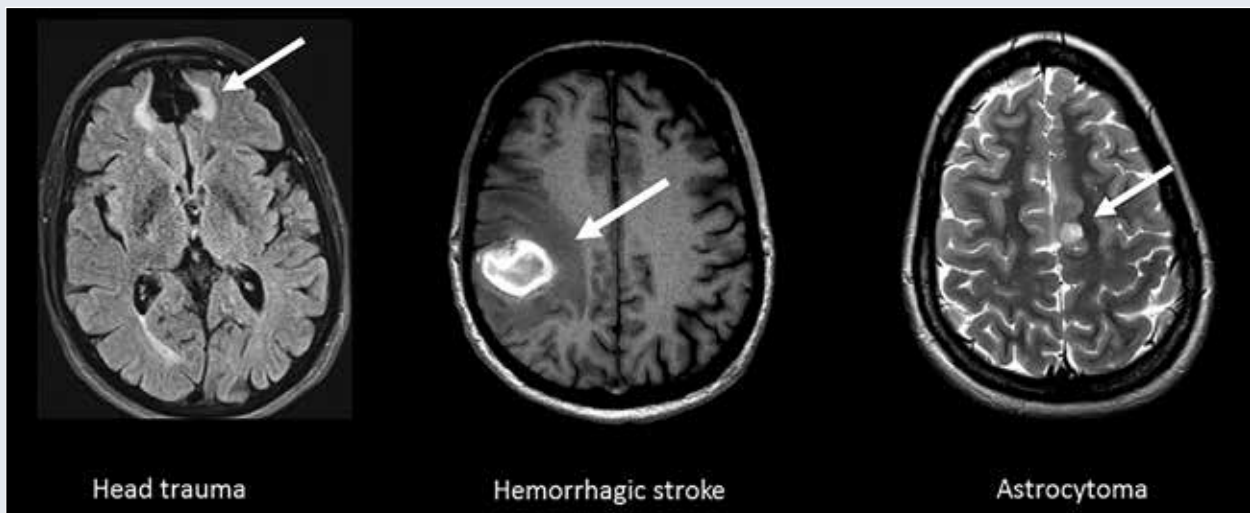
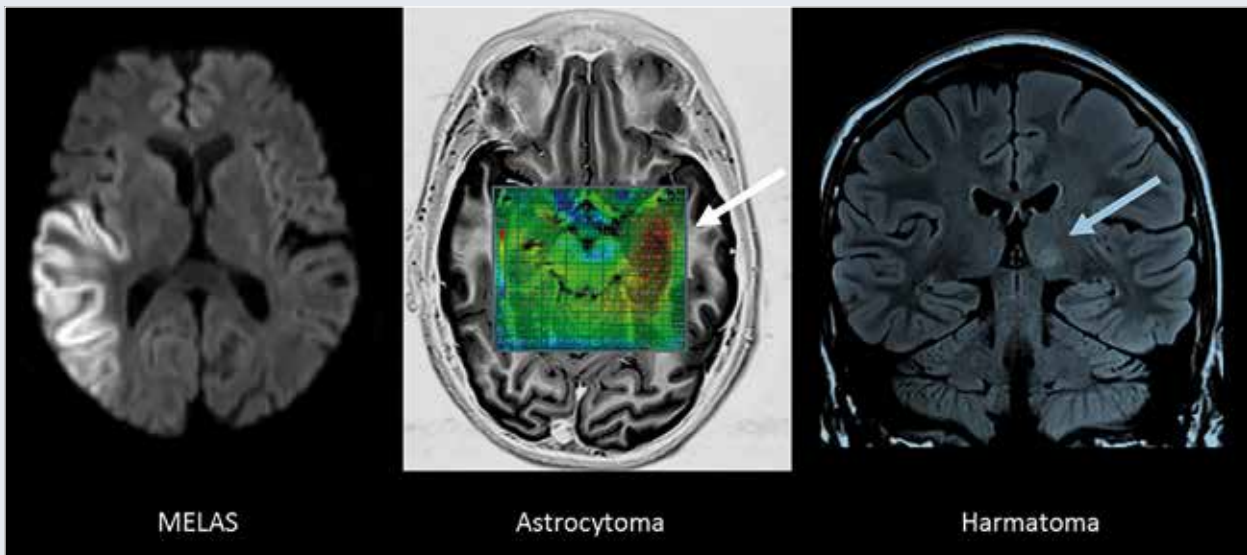


Figure 3: Typical imaging findings in patients with first seizure, Left: FLAIR image with bilateral fronto-polar/fronto-mesial chronic lesions after head trauma. Middle: Right cortico-subcortical subacute haemorrhage on T1-weighted image. Right: T2-weighted image showing a T2-hyperintense tumor adjacent to cortical tissue of the left SMA. Cortical involvement of the lesion indicates epileptogenic potential.





**Figure 4: Typical imaging findings in patients with first seizure (cont.)** Left: Diffusion restriction on DWI in the right temporal lobe in a patient with MELAS. Middle: MR-Spectroscopy unveiling a astrocytoma in the left mesiotemporal structures by documenting increased cholin concentrations within the tumoral tissue. Right: Diencephalic hamatoma on FLAIR image.

ing to the new epilepsy definition requirements – is currently restricted to lesions that are sequelae of an insult to the brain. For brain lesions such as low grade gliomas, cavernomas and AVMs, mesiotemporal sclerosis and malformations of cortical development the 10 years seizure recurrence rates have not yet been specifically studied. Hence, the presence of these brain lesions does not fulfill the requirements of the current criteria to replace a second unprovoked seizure [1] (see **Figure 5** for illustrative cases). Clearly, more epidemiological data are required to further translate the current imaging definitions from a “potentially epileptogenic structural brain lesion” into a “predictive brain lesion for recurrent seizures”. Notably, almost 50% of the brain lesions detected during the workup of a first seizure may nowadays be considered as incidental. Thus, the imaging result has to be always balanced towards the personal situation of the patient and the type of lesion in the discussion if an antiepileptic treatment has to be started of a single seizure. A growing low-grade CNS tumor may be resected for neuro-oncological reasons, yet not due to its epileptogenicity. A diagnosis of epilepsy carries severe consequences for the individual patients and may be difficult to be reversed. Hence, even in case of “potential epileptogenic lesion” on neuroimaging, waiting for seizure recurrence prior to making a diagnosis of epilepsy may still be appropriate. Neuroimaging under emergency conditions is required to inform the epileptologist about potentially treatable conditions related to the seizure and to decide whether a presumably unprovoked seizure may turn into a provoked one (which alters the prognosis). Further, elective neuroimaging should be performed in every patient with focal abnormalities on EEG, focal neurological deficits and focal seizure onset. MRI can be omitted in clear cut cases of genetic generalized epilepsies. If MRI is requested,

the qualitative requirements should be targeted toward the detection of epileptogenic lesions, thus following epilepsy protocol standards that warrant further postprocessing and lesion analysis.

#### **d. Are newer imaging techniques available which are promising to increase the diagnostic yield?**

As discussed above the application of the new definition of epilepsy requires epidemiological data on seizure recurrence rates in 10 years that are not available for a large portion of clinic situations after a first seizure. In parallel new imaging techniques emerged in recent years, for example brain perfusion measurements, susceptibility weighed imaging (SWI), simultaneous EEG/fMRI recordings and neuronal current imaging (NCI) or various nuclear medicine techniques e. g. PET measurements. All these new techniques have been applied to epilepsy. Currently, knowledge of the diagnostic benefit of these techniques are based on case studies. In the following we will give illustrative examples of different imaging approaches and discuss the potential of these techniques that could be selectively used in patients.

Brain perfusion measurements on CT or MRI are part of the emergence imaging protocols in the majority of hospitals in Switzerland. In cases of unwitnessed episodes of seizures, persisting altered mental state or focal deficits, acute stroke has to be ruled out during the emergency situation. Epileptic brain activity induces hemodynamic changes which can be detected on perfusion measurements. A hyperperfusion can be identified in the majority of cases during nonconvulsive status epilepticus [10] (**Figure 6**). The “epileptic” hyperperfusion has a cortical distribution, is not related to

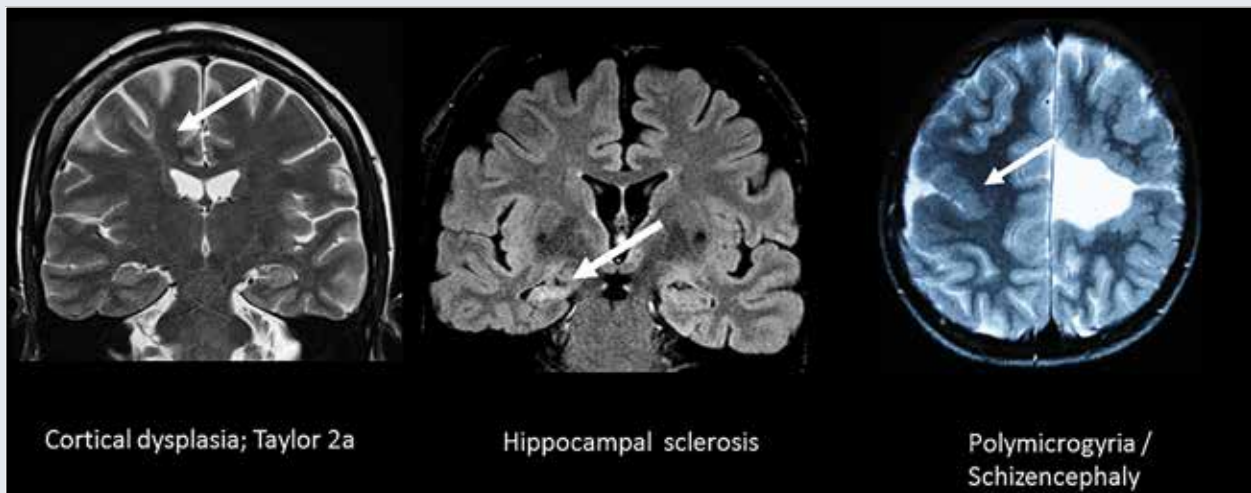


Figure 5: Imaging findings in specific epilepsy syndromes, Left: Juxta-cortical T2 hyperintense lesion (transmantle sign) in the cortical dysplasia Type Taylor 2a. Middle: FLAIR hyperintense and atrophic hippocampal formation in hippocampal sclerosis in mesiotemporal epilepsy (MTLE). Right: Inborn polymicrogyria / schizencephaly in Lennox-Gastaut syndrome.

vascular territories and should motivate an immediate electro-clinical evaluation. In the postictal state, especially during a Todd's paresis or aphasia, brain hypoperfusion can be visualized. The distribution of the "epileptic" hypoperfusion of postictal state is unrelated to the vascular territories and in general covers the whole hemisphere. In emergency setting epilepsy-related perfusion alterations may guide diagnostic workup. Data on treatment decisions and outcome are not available.

Another recently established imaging technique is the susceptibility weighted imaging (SWI). This technique is sensitive to the paramagnetic effect of the imaged tissue. Hemosiderin and calcifications are the main target of SWI but changes in deoxygenated blood content in veins are as well visible. In a recent study, our group reported the potential to detect focal and generalised hyperperfusion in status epilepticus by SWI [11]. The presence of hypointense veins as potential correlate to nonconvulsive status epilepticus (NCSE) may – like perfusion measurements detecting a hyperperfu-

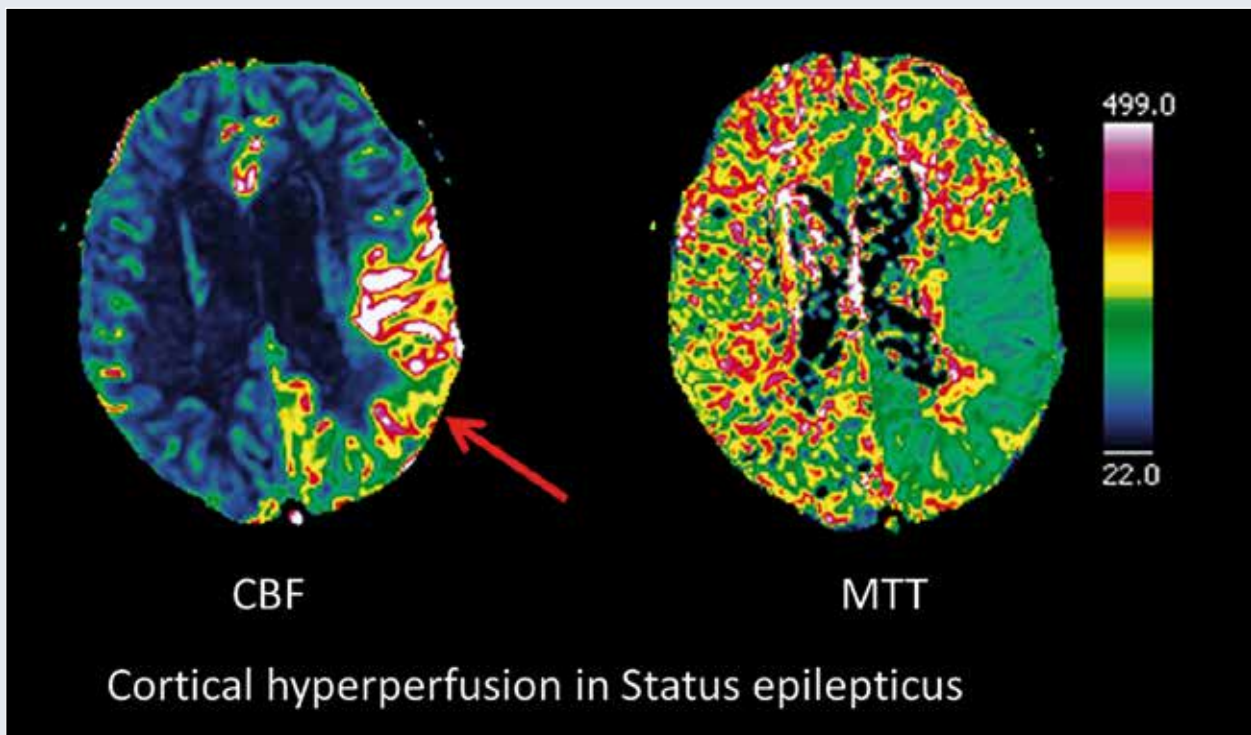
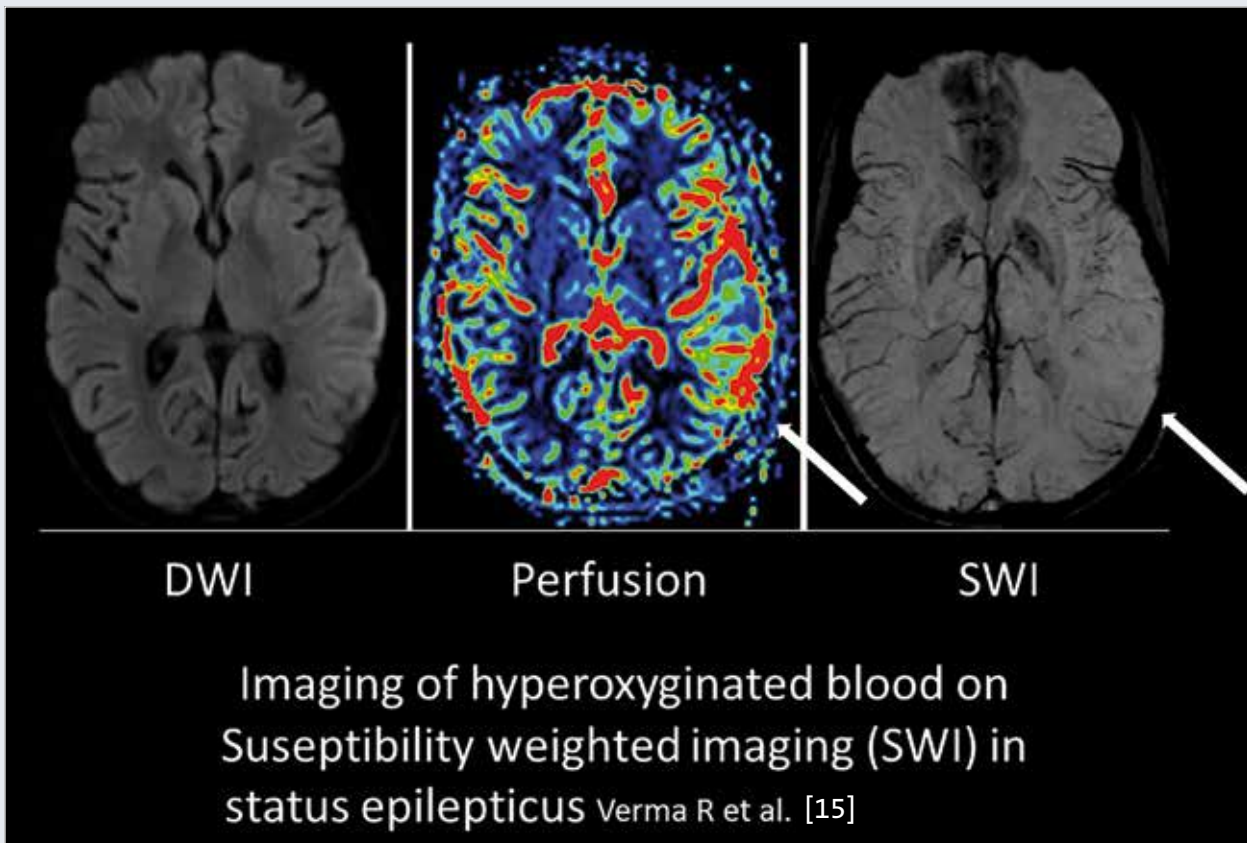


Figure 6: Perfusion measurement during NCSE, Hyperperfusion (red arrow) in NCSE visualized by increased cerebral blood flow (CBF) left side and reduced mean transit time (MTT) right side.



**Figure 7:** SWI showing on the right side disappearance of hypointensive signal in cortical veins in the region of ongoing hyperperfusion (middle image) during non-convulsive status epilepticus. The diffusion weighted imaging (DWI) (left image) detects a diffusion restriction within the symptomatogenic zone as defined by the perfusion imaging of the current status epilepticus.

sion – lead to an immediate EEG recording to establish the diagnosis of NCSE. The diffusion weighted imaging (DWI) changes do most likely indicate parenchymal damage, however the prognostic role of epilepsy related diffusion changes in respect to seizure recurrence and cognitive outcome has to be established (see **Figure 7**).

Recording EEG signals inside the MR scanner during BOLD measurements is called simultaneous EEG/fMRI. Analysis correlates hemodynamic changes to epileptiform EEG activity and is an established tool in epilepsy research and progressively gaining importance in the presurgical epilepsy workup [16]. The examples given here, highlight additional information from EEG/fMRI in two patients with similar clinical and EEG findings consisting in generalized seizures and diffuse interictal epileptic spike-wave activity on surface EEG after first seizure. In the first patient simultaneous EEG/fMRI recording shows a focal hemodynamic change in frontal operculum as correlate to a frontal lobe epilepsy with rapid generalisation (image on the left side). In the second patient (image on the right side) a generalized pattern of hemodynamic changes with positive BOLD correlate in the thalamus point to an underlying generalized genetic epilepsy (**Figure 8**).

The imaging techniques based on perfusion changes in the brain as perfusion measurements itself, SWI or EEG/fMRI rely on measuring indirect effects of the epileptic neuronal activity. The Neuronal Current Imaging (NCI) has been developed in our group aiming at visualising neuronal activity directly on MR images [17]. The underlying principle is that the distortion of the magnetic field as induced by electric currents arising from high frequency neuronal activity is depicted by an MRI sequence adapted from magnetisation transfer imaging protocols. A first study shows encouraging results in lateralising of the epileptic activity. In most of the cases the seizure onset zone was located in the lobe of activation in the NCI. Interestingly, in patients with drug-resistant epilepsy with a favourable outcome after surgery NCI activity has disappeared on the postoperative MRI. The example given here, shows the spatial concordance of the distribution of the amplitude mapping of interictal spikes and the localisation of the NCI measurement (**Figure 9**). Clinical relevance of NCI needs to be established by consecutive studies and experiences.



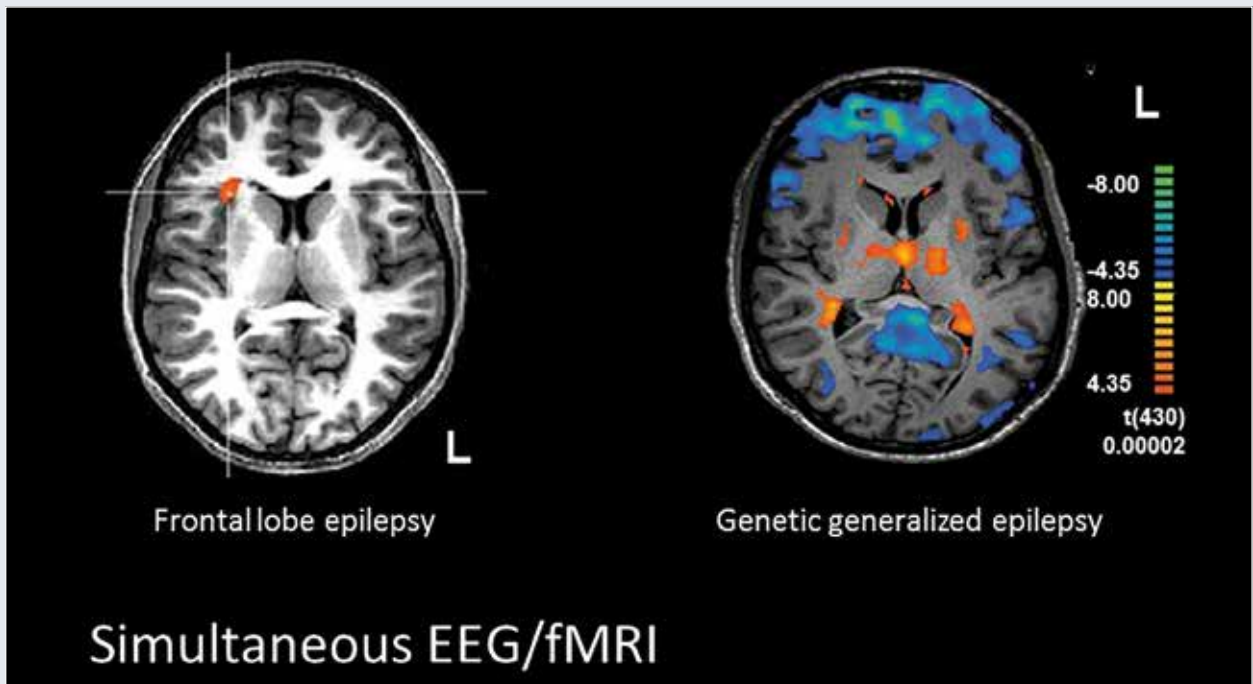


Figure 8: Simultaneous EEG/fMRI with different findings in focal epilepsy and genetic generalized epilepsy (for details see text).

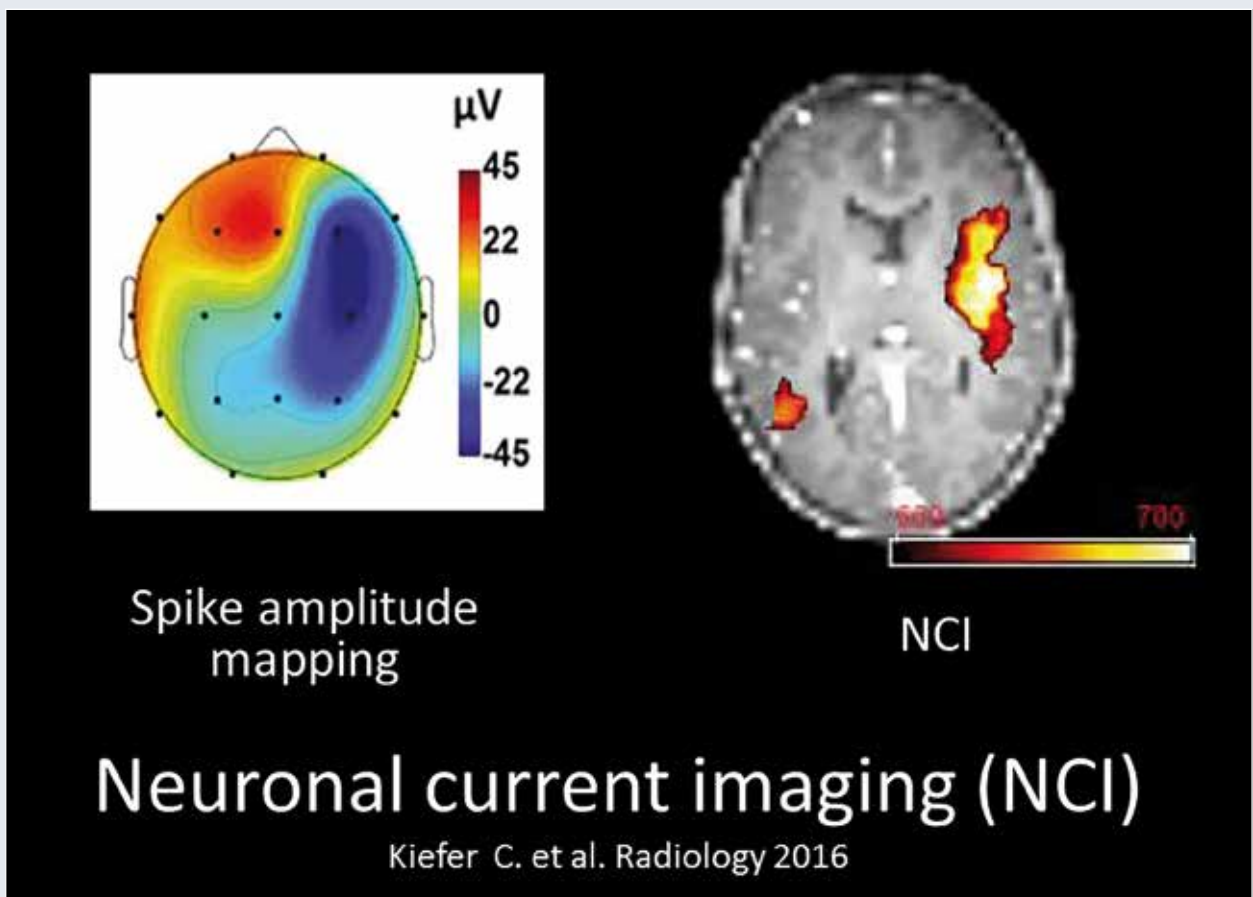


Figure 9: Neuronal current imaging (NCI) as first imaging technique directly related to neuronal activity shows activity in the accordance to epileptic EEG signals.



## Summary

Neuroimaging is one of the main pillars of diagnostic workup in epilepsy. After a first seizure neuroimaging is indicated in all patients but those presenting with a typical genetic generalized epilepsy. Emergency imaging is warranted if the seizures may be the symptom of an acute brain pathology. If the patient returns “back to baseline” at the time of clinical examination, MR imaging may be performed electively using a dedicated epilepsy protocol. Data on seizure recurrence rates over 10 years is still lacking for many classical brain pathologies associated with epilepsy. Novel imaging techniques may be helpful in detecting prolonged seizures and mimics in the emergency setting.

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**Address for correspondence:**  
**PD Dr. med. Martinus Hauf**  
**Support Center of Advanced Neuroimaging (SCAN)**  
**University Institute of Diagnostic and Interventional**  
**Neuroradiology**  
**University of Bern, Inselspital**  
**CH 3010 Bern**  
**Phone 0041 32 338 4125**  
**Fax 0041 32 338 4008**  
**Hauf.M@klinik-bethesda.ch**