Purpose of review
Epilepsy research has extended from studies at the cellular level to the investigation of interactions of large neuronal populations distant from one another: ‘epileptic networks’. This article underlines the concept of epilepsies as network disorders, adding empirical evidence from electroencephalography-combined functional MRI (EEG-fMRI) studies.

Recent findings
These noninvasive in-vivo EEG-fMRI epilepsy studies have characterized the ictal temporal–spatial evolution and the interictal persistence of altered activity in typical sets of (sub)cortical brain regions responsible for the clinical manifestation of the disease and its underlying encephalopathy, for example, thalamus vs. cortex in generalized; hippocampus vs. cortex in temporal lobe; a frontal near-piriform region universally in focal epilepsies. Models exist validated against intracranial EEG that can explain interictal and ictal activity based on statistical coupling between different brain regions, and if extended could guide the design of new treatments.

Summary
The appreciation of epileptic processes at the network level will foster the development of both anticonvulsive as well as true antiepileptic treatment strategies locally modulating hub regions within the epileptic network architecture as well as entire networks by targeting their characteristic properties such as neurotransmitter or neuronal firing profiles. Treatment should reach beyond seizure control and include the improvement of cognitive function.

Keywords
epilepsy, heuristic, model, network, treatment

INTRODUCTION
This article will present a network heuristic of epilepsy amalgamated from studies and concepts mainly published within the last 18 months. An example for a network concept based on stereotactic electroencephalography (EEG) will be given [1**], and the link between associated synchronized neuronal activity and the functional MRI (fMRI) signal will be sketched, before surface EEG-derived blood oxygen level-dependent (BOLD) maps are interpreted as large-scale networks lending empirical support to the heuristic. Like the zone concept is helpful in epilepsy surgery, so the network concept can become relevant for the treatment of epilepsy, provided the heuristic will grow into a proper model that can describe the disorder and make predictions on its course and the effect of interventions.

THE ZONE AND NETWORK CONCEPTS OF EPILEPSY
About 10 years ago, Rosenow and Lüders [2] reviewed the zone concept of epilepsy that has helped to conceptualize seizure disorders especially in the context of presurgical patient evaluation: the symptomatogenic zone (area of cortex producing ictal symptoms); the irrigative zone (area of cortical tissue that generates interictal spikes); the seizure onset zone (area of the cortex from which seizures are generated); the epileptogenic lesion (radiographic lesion that is the cause of the epileptic seizures); the epileptogenic zone (area of cortex indispensable for seizure generation); the functional deficit zone (the area of cortex that is functionally abnormal in the interictal period); and the eloquent cortex (cortex related reproducibly to a given...
As the seizure develops, the signal frequency gradually slows down, the amplitude progressively increases, and activity becomes more rhythmic and synchronous across the recorded regions. During this ‘clonic phase’ clinical symptoms can be observed. Finally, a few tens of seconds after the initial EEG changes, the seizure terminates abruptly on all channels [1**]. These observations, hand in hand with additionally presented model data, represent an example for different oscillations leading to spread of activity across regions and synchronous activity that binds regions together as networks. Simultaneous hemodynamic and stereotactic EEG recordings are meanwhile technically feasible [11**,12] and should hence soon reveal the exact fMRI correlates of the mentioned synchronized activity. Concurrent electric source imaging with fMRI suggests that EEG-derived BOLD maps represent epileptic network activity reflected in the EEG [8,13,14], most likely induced by synchronized neuronal oscillatory activity, for example, in the local field potential gamma band [15,16]. EEG-combined fMRI (EEG-fMRI) has the advantage over invasive stereotactic EEG that full brain coverage is standard making possible the identification of distributed large-scale networks. Hamandi et al. [7] in a patient with refractory temporal lobe epilepsy showed activation in association with left anterior temporal interictal discharges in the left temporal, parietal, and occipital lobes. Using effective connectivity analysis of EEG-fMRI data and tractography, they demonstrated propagation of neural activity from the temporal focus to the area of occipital activation.

A SIMPLIFIED DESCRIPTIVE NETWORK HEURISTIC

A network heuristic, or concept, of epilepsy should be compatible with the following phenomena – and after detailed refinement eventually become a model able to explain them: onset and offset of individual seizures and the seizure disorder; ictal and interictal electrophysiological phenomena; ictal clinical behaviour (seizure semiology); interictal clinical behaviour (cognitive alterations); and reaction to different treatments.

Still far from being a macroscopic model [17], a simple descriptive network heuristic could be the following: genetic abnormalities directly or indirectly cause irregularities in neuronal excitability, for example induced by channelopathies [18], receptor mutations [19], other neurometabolic dysfunctionality [20], or structural malformations [21], leading to local or distributed changes in the brain in the form of imbalances within neuronal function. Although not expressed as such, the recognition of this set of regions responsible for seizures with interregional interaction already implied a network concept of seizures, and in particular epilepsy, because the description of a functional deficit zone implies a persistent condition.

The network idea is not new. In 2002, for example, Spencer [3] expressively presented a concept of human epilepsies as disorders of large neuronal networks, which she defined as ‘functionally and anatomically connected, bilaterally represented set[s] of cortical and subcortical brain structures and regions in which activity in any part affects activity in all the others’. On the basis of clinical observation, intracranial EEG, functional neuroimaging, anatomical studies, and treatment response, Spencer exemplified three such networks. Extending this concept, Halasz and Rasonyi [4] highlighted the relevance of the thalamocortical network in generalized epilepsies and of those apparent in childhood epilepsies, pointing out interactions of network activity with physiological (e.g. sleep) or maturational (explaining spontaneous remittance) processes within the brain. Computational models [5] and connectivity analyses applied to different modalities have since added direct evidence to this observational level [1**,*6–10] as will be exemplified in the following paragraph.

Wendling et al. [1**] provide evidence, both at the computational model as well as the empirical level, for typical oscillatory patterns associated with interregional connectivity and network formation. For example, in stereotactic EEG recordings of mesial temporal lobe seizures, they describe initial appearance of a fast activity in mesial structures. Next, higher frequencies in the low gamma band (20–30 Hz) follow for generally between 5 and 10s.
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systems, activity in some of which potentially manifesting as seizures. Alternatively, secondary structural brain damage such as immunological, induced by trauma or ischemia can cause analogous disorder. The resulting imbalances are either directly situated within or can influence one or several physiological networks of the brain, such as can be identified during rest \cite{22}. Activity within a physiological network is then periodically or continuously influenced, and consequently by or with it additional networks. This causes a periodic or continuous change in network activity with associated dysfunction – either in the form of interictally compromised brain function (e.g. cognitive impairment) \cite{23,24}, or of an overt seizure depending on the network involved and the degree of imbalance caused therein. At the modeling level, such network behaviour would equal a move of a system through parameter space \cite{5}. Which and whether, or to what degree, a network is ‘vulnerable’ to undergo the described transition depends not only on the degree of primary disorder within or influencing the network but also on other contexts such as the vigilance or cognitive state of the individual as well as binding with other networks and firing modes of communicating (subcortical) brain regions \cite{28}. Cessation of a seizure can then be induced within any of the elements involved at multiple levels \cite{30}, eventually restoring system balance to a degree at which no overt seizures occur.

Of note, the idea is that several networks interact with one another and intermittently more networks are recruited to or disengage from this set, explaining seizure onset, ictal behaviour, seizure cessation, as well as interictal phenomena. In other words, different features of the epilepsy might be linked to different and individual networks, although the typical set of interacting networks characterizes the particular epilepsy syndrome. In the following, some aspects of the network concept shall be elaborated further.

Onset and cessation of epilepsy and seizures

Naturally, scarce longitudinal data exist that assess network properties before and after the manifestation of epilepsy. However, in a single child with epileptic encephalopathy, the disruption and (surgical) restoration of physiological brain function were nicely demonstrated based on fMRI functional connectivity analysis: due to a seizure disorder, behavioral regression occurred accompanied by an abnormal EEG pattern with high-amplitude, disorganized slow activity with frequent generalized and multifocal epileptiform discharges. Concomitantly resting-state functional connectivity MRI showed reduced BOLD fluctuations and lack of normal connectivity. After successful corpus callosotomy for treatment of drop seizures, the child’s behavior returned to baseline with a normal background waking EEG and functional connectivity MRI restored to normal \cite{31}. Depending on the maturational state of the brain, vulnerability to epileptic phenomena temporarily increases \cite{32} with either subsequent recovery \cite{33} or chronic manifestation \cite{33,34}. One example of the latter process in the temporal lobe has been described in the context of gamma-aminobutyric acid (GABA)-dependent high frequency oscillations (80–120 Hz) ‘infecting’ previously healthy tissue with the property of endogenously giving rise to epileptic activity according to the notion that ‘seizures beget seizures’ \cite{34}.

Ictal and interictal electrophysiological phenomena

In this section, it first shall be highlighted that ictal studies indicate seizure-associated involvement of different sets of brain regions and that fMRI signal behaviour can be linked to electrophysiological phenomena. Subsequently, hemodynamic changes linked to interictal EEG will be presented.

BOLD maps of seizures have been created in a variety of seizure types and with different methodology \cite{35}. BOLD signal changes have been observed preceding ictal clinical or scalp EEG changes as well as others outlasting them; also, differential BOLD patterns were observed during different phases of a seizure \cite{35}. For example, Thornton et al. \cite{36} in seven of nine patients found significant BOLD signal changes early during the seizures and concordant with the seizure onset zone as defined using intracranial EEG. They proposed that additional BOLD signal changes that they observed during clinical ictal and late ictal phases paralleled the spread of ictal EEG activity on EEG. At this macroscopic level, ictal fMRI studies are hence congruent with the proposition of an evolution of seizure-associated spatially distributed activity, that is, a network concept of epilepsy.

Traditionally, interictal EEG-correlated BOLD signal changes were thought to represent the irritative zone \cite{2}, and EEG-MRI results in epilepsy studies were and often still are discussed in the context of the zone concept. Of note, usually the location of the statistical maximum of BOLD signal changes in multiple regions is discussed but per se does not exclude the presence of a ‘network’ of regions simultaneously active. The observation and modeling of synchronized high-frequency EEG activity \cite{1} representing the connection of different brain regions can be assumed to cause the BOLD signal changes detected in ictal EEG-fMRI studies – be it in the form of early or preictal signal alterations without
any scalp EEG correlate or those associated with ictal scalp EEG changes that themselves originate from highly synchronized neuronal activity.

Interictal electrophysiological changes at the scalp level can be observed in the form of abnormal ongoing (i.e. spontaneous) background activity and interictal epileptiform discharges. Although the latter can be directly modeled as events like in ‘classic’ EEG-fMRI studies [25, 27, 37–39], the former should best reverberate in alterations of resting-state fMRI activity [40]. Indeed, Bettus et al. [6] examined interictal functional connectivity of human epileptic networks (epileptic and unaffected regions) with intracerebral EEG and fMRI. Functional EEG-based connectivity was higher in regions affected by electrical epileptiform abnormalities compared to nonaffected areas, while BOLD signal-derived functional connectivity behaved inversely. Although this suggests differential effects of epileptic phenomena on electrophysiological and hemodynamic signals, it confirms the existence of fMRI sensitivity to interictally altered network dynamics. Moreover, Bettus et al. [6] found that the epileptogenic regions influence the nonepileptic areas during the interictal period. Structural and functional changes in networks measured during the interictal resting period were also demonstrated using graph theoretical analysis [41, 42]. Negishi et al. [43] proposed functional MRI connectivity as a predictor of epilepsy surgical outcome.

Recently, we reported converging PET and fMRI evidence for a common area involved in human focal epilepsies that by nature of the analysis in the network context can be interpreted as a hub, that is, an intersection common to overlapping networks [44]. Time-locked with interictal epileptiform discharges, we found significant hemodynamic increases common to all patients near the frontal piriform cortex ipsilateral to the presumed cortical focus. GABA (A) receptor binding in the same area was reduced in patients with more frequent seizures. These findings of cerebral blood flow and GABAergic changes support the notion of persistent interictal network changes modified by seizure activity and delineate a potential universal therapeutic target.

**Ictal clinical behaviour (seizure semiology)**

In the following, an overview will be given of fMRI studies identifying characteristic networks associated with typical seizure semiologies [4, 28**, 29].

Numerous studies exist pointing out a thalamocortical network in primary and secondarily generalized epilepsies [45–47]. Salek-Haddadi et al. [48] were the first to describe, with fMRI, subcortical and cortical structures involved in absence seizures, identifying thalamic BOLD signal increases and symmetrical, widespread cortical signal decreases maximum in the frontal lobes related to absence seizures. Later, Moeller and colleagues – among others [49] – demonstrated individual differences between patients beyond the mentioned group-conserved findings, including apparently early – despite variable – signal changes in precuneal and frontal cortices preceding thalamic activity changes suggestive of a cortical lead in this epilepsy syndrome [50–53]. Similarly, Vaudano et al. [54] had presented evidence for a causally permissive role of the precuneus for the generation of generalized spike and wave discharges.

The behavior during absences and complex partial seizures has much in common with other disorders of consciousness resembling a transient minimally conscious state [55]. This requires altered cortical function that can occur either directly from disorders that impair widespread bilateral regions of the cortex or indirectly through effects on subcortical arousal systems. Electrophysiological observations suggested a ‘network inhibition hypothesis’ in which subcortical arousal systems that normally maintain default mode network activity in the wake state are actively inhibited by seizures resulting in deactivation of cortical areas [56, 57].

Numerous other epileptic networks have been identified with EEG-fMRI. In children with photoparoxysmal response, EEG gamma activity-associated fMRI signal changes were described in a part of the frontoparietal visual network responsible for saccades and visual attention [58]. Seizure-related BOLD signal changes revealed networks in fixation-off sensitivity in parietooccipital regions [59–61]. In musicogenic epilepsy, left anterior temporal lobe [62], right dorsal frontal cortex, and right temporal lobe [63] exhibited BOLD signal changes in response to epileptogenic music. In reading epilepsy, fMRI identified the motor and premotor cortex, striatum, mesial temporal lobe, and thalamus in relation to orofacial reflex myoclonus and reading-induced EEG discharges [64]. In a patient with epilepsy partialis continua of the hand, Vaudano et al. [14] recently demonstrated ictal spike-associated activity changes in the motor network (central gyrus, prefrontal cortex, and cerebellum).

**Interictal clinical behaviour**

Cognitive and psychiatric impairment affect half of all epilepsy patients and represent the main clinical manifestations of pathological interictal behavior [65–67]. Factors contributing to cognitive dysfunction are the type and frequency of seizures, the location of underlying brain lesions (epilepsy
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syndrome), and anticonvulsive drugs [68]. Effects can be ‘indirect’ in that they alter sleep physiology and via this mechanism induce disorder, for example, memory deficits [69]. Altered sleep is another example of disturbed network function caused by epilepsy. The interaction of sleep and epilepsy can easily be observed: many grand mal or frontal lobe seizures occur upon awakening or in sleep, respectively; interictal discharges can occur exclusively during sleep, or their frequency is sleep stage-dependent [70,71]. Research has progressed in identifying mechanisms common to epilepsy and sleep [28**,29,72,73]. In particular, the (reticular) thalamocortical network also involved in the generation of sleep spindles and K complexes [74–76] was repeatedly found to be active during generalized spike and wave discharges.

A similar pattern of subneocortical activation and (inverse) cortical activation was found in a group analysis of patients with temporal lobe epilepsy syndromes of different cause (mesial or neocortical, sclerosis, scar, or tumour) [77]: interictal discharges at the group level correlated with hippocampal fMRI signal changes ipsilateral to the supposedly lesioned hemisphere. Cortical changes – like in the EEG-fMRI studies of generalized epilepsy syndromes – largely overlapped with default mode brain regions speculated to be responsible for interictal cognitive impairment [23,77,78]. It has been suggested that the hippocampus may reflect a common relay station in temporal lobe epilepsy with some analogy to the role of the thalamus in generalized epilepsies [27]. The widespread deactivations in default mode brain regions, both in focal and generalized epilepsies and the finding of fMRI signal changes in regions remote to the presumed origin of the interictal EEG discharges are in keeping with the concept of one – or more – epileptic network(s) involved and eventually responsible for ‘interictal encephalopathy’ [70,78,79].

Reaction to different treatments

In the proposed network heuristic, features of the ‘zones’ [2] clearly reverberate as properties of ‘networks’. In the surgical zone concept, the removal of the epileptogenic zone – defined post-resection – leads to seizure freedom as it can overlap with any of the other regions. Similarly, in the network concept, both endogenous or exogeneous modulation resulting in seizure interruption or prevention can occur anywhere in any one or several of the networks involved. The heuristic particularly motivates the identification of multiple networks and network modules (sets of regions within networks) to be targeted in parallel and especially not necessarily only in the form of resection. Interventions should affect both interictal and ictal network activity, and ideally true antiepileptic in addition to anticonvulsive treatment could be developed [80,81]. Potential interventions include those modulating intrinsic – including per se physiological – network constants responsible for, for example, neurotransmission and oscillations as well as network interactions (anatomical links, functional architecture, binding) by means of pharmacology [80–83], electrical stimulation [84–87], surgery [88–90], and modulation of brain state (e.g. biofeedback, strategies affecting the level of vigilance) [91,92].

CONCLUSION

According to the network heuristic, the set of involved networks will determine the clinical epilepsy syndrome and responsiveness to different treatments. The heuristic does not distinguish between focal and generalized epilepsies [28**,29,93]. The more networks get involved in the condition, the more variable the clinical picture and less predictable the treatment response (and any joint network behaviour) will become due to resulting complex interactions. Still, an initially dynamic disease as typically observed in childhood epilepsy over time can turn into a more stable adult form reflecting that the set of epilepsy-defining networks has reached a steady state. This equilibrium can be perturbed again by a multitude of internal [e.g. fever, sleep (pressure), brain maturation, metabolism] or external (e.g. chemical, electrical, surgical intervention) factors leading to ‘remodeling’ of the networks at the cellular, molecular, structural, or functional level. Conceptualizing epilepsies as disturbed network interactions motivates – and requires – the development of multitarget and modal treatments acting on these networks including physiological ones. In-silico computational and modeling methods [5,17] need to be improved further as they should pave the way to the design of literally antiepileptic therapeutic strategies [80,82,83,94]. Meanwhile, clinicians should remember that epilepsy is ‘always on’ and all effort should be made not only to achieve seizure control but also to alleviate interictal disorder requiring multidimensional treatment.

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Conflicts of interest

There are no conflicts of interest.
REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 213).


12. Simultaneous intracranial EEG and IMRI is feasible if necessary precautions are respected. This method bears great potential to characterize the different BOLD responses to different neuronal oscillations as measured by invasive EEG, which should lead to an improved interpretation of noninvasive EEG-IMRI studies.


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