

# Understanding ictogenesis in generalized epilepsies

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Generalized seizures are defined by bilateral symmetric and synchronous epileptiform EEG discharge over the entire convexity and commonly thought to involve the entire brain homogeneously. The characteristic 3–3.5 Hz Spike-and-Wave pattern is conceived as a resonance phenomenon originating in a cortico-thalamic circuit where it can start at variable sites. Investigations with EEG source analysis, magnetencephalography, positron emission tomography and single photon emission computerized tomography, functional magnetic resonance imaging and transcranial magnetic stimulation have suggested that generalized seizures have cortical onset and the thalamus has an essential role in the recruitment of a network comprising frontal, parietal and occipital cortex and the default mode network. Studies of reflex epileptic traits have shown that ‘generalized’ ictogenesis largely uses pre-existing functional anatomic networks normally serving physiological functions. It has therefore been proposed to consider these epilepsies as system disorders of the brain. Treatment is fundamentally pharmacological with a role for behavioral interventions. Generalized epileptic encephalopathies of early childhood are sometimes surgically remediable.

**KEYWORDS:** cortico-thalamic network • default mode network • epileptic network • functional imaging • generalized epilepsy • ictogenesis • reflex epilepsy • source analysis • system epilepsy

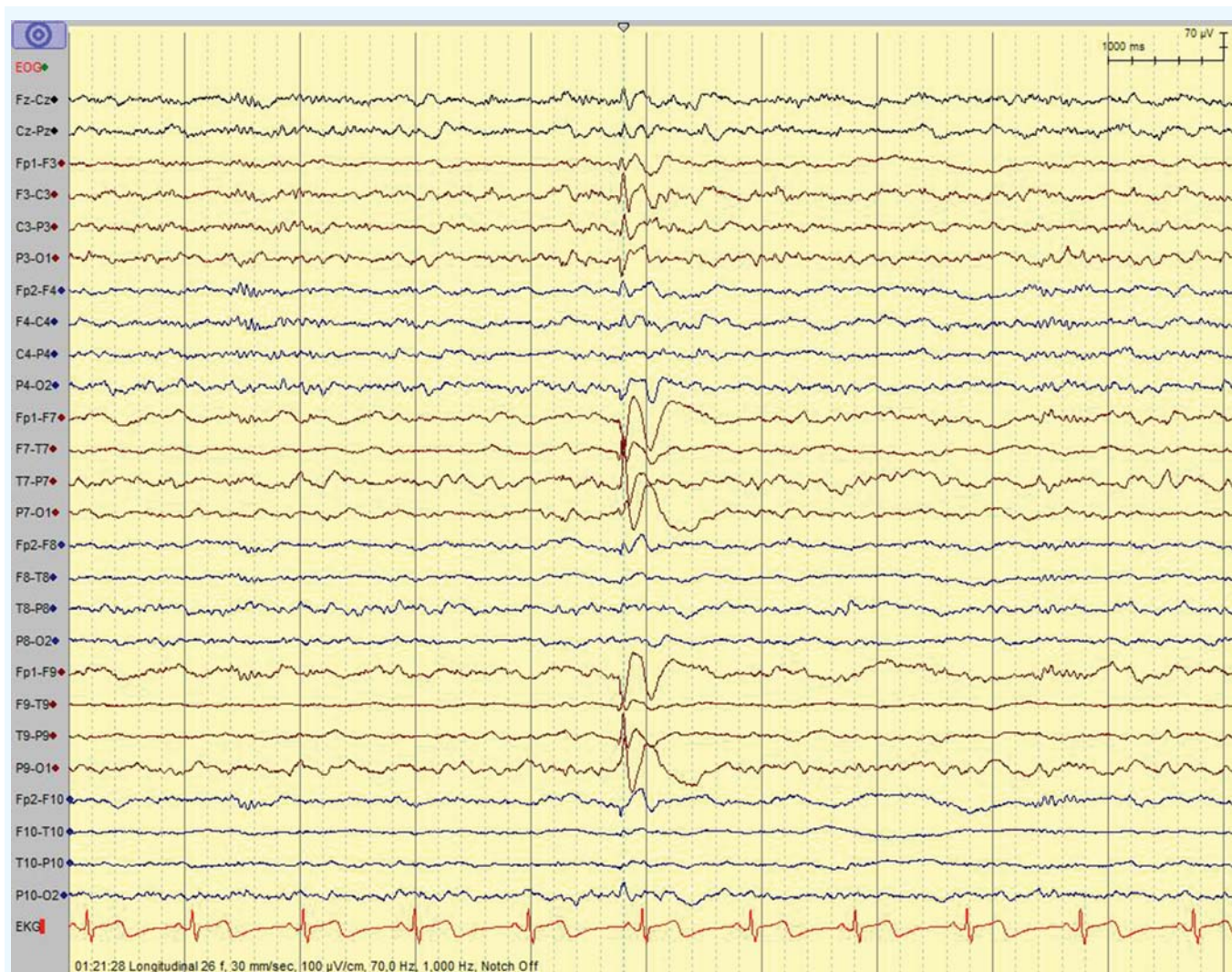
Epileptogenesis refers to the processes by which epilepsy is established in a brain and ictogenesis, to the processes generating individual seizures in an epileptic brain. For a long while, our understanding of the latter has been very vague, especially considering those bilateral symmetrical seizures without apparent local onset, which have been termed ‘generalized’ [1]. Over the last decade, this situation has fundamentally changed in consequence of a series of findings with new and advanced investigations. These converge to shape a new understanding of generalized ictogenesis of which at least the contours have become apparent. It seems, therefore, timely to review these developments.

## Early views of generalized ictogenesis

Historically, until long into the 19th and even 20th centuries, epilepsy was mostly considered as synonymous with ‘Grand mal’ seizures, that is, convulsive seizures with loss of consciousness and affecting the entire musculature, which are today called generalized tonic–clonic seizures (GTCS). Many possible causes were proposed, but the views on ictogenesis, that is, the generation of individual seizures in the brain, remained rather vague. When Hughlings Jackson became aware

of the local cortical onset of some seizures, he did not consider these as a different category but defined epilepsy ‘as a condition in which there is a sudden excessive transitory discharge of some part of the cortex’ ([2], p. 9). However, his cooperation with the neurosurgeon, Victor Horsley, also gave rise to the concept of focal seizures and a surgically removable ‘epileptogenous focus’ ([2], p. 380).

A landmark event for the nosological understanding of the epilepsies was the advent of EEG, which revealed that, fundamentally, two types of epileptiform discharge existed. One type was consistently localized spikes or sharp waves at the anatomical site of origin of focal seizures (FIGURE 1). The other type was widespread bilateral symmetric and quasi-synchronous trains of spikes followed by a slow wave (the Spike-and-slow wave pattern) in rhythmic repetition at a frequency of mostly 3–3.5 Hz (FIGURE 2). The impression on the scalp EEG that this spike-wave (SW) pattern involved the entire convexity gave rise to calling it a generalized discharge. In consequence, the seizures and epilepsies for which this pattern were characteristic (including minor seizure types like absences and brief bilateral myoclonic jerks without impairment of



**Figure 1. Focal epileptiform discharge.** Sharp wave followed by a slow wave in the left temporal region (maximum negativity in the anterior–inferior temporal region). Longitudinal bipolar montage including electrodes in the inferior temporal row (scale: 1 s × 70 µV).

consciousness) came now also to be termed as generalized. The underlying understanding is reflected in the definition of generalized seizures in the 1970 ILAE Clinical and Electroencephalographical Classification of Epileptic Seizures: “Clinical features do not include any sign or symptom referable to an anatomical and/or functional system localized in one hemisphere. The responsible neuronal discharge takes place, if not throughout the entire grey matter, then at least in the greater part of it and simultaneously on both sides” [1]. The resulting common view was that generalized seizures involved the entire brain homogeneously [3], whereas in clinical neurological jargon, a ‘generalized seizure’ still often is used as a synonym for a GTCS.

### The concept of thalamocortical epilepsy

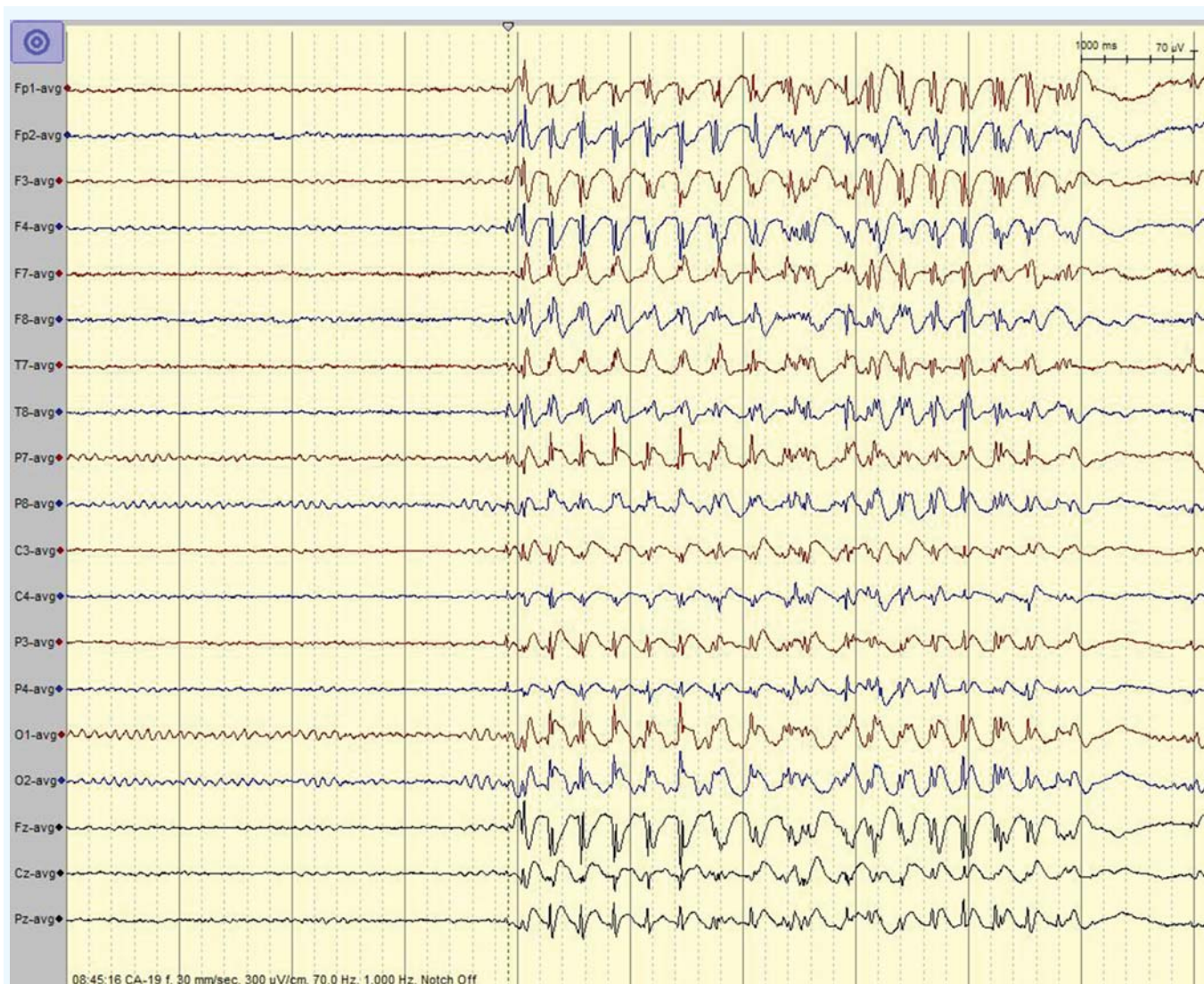
The discovery of simultaneous and quasi-symmetric bilateral SW discharge rapidly generated a debate whether its origin was cortical or subcortical. Animal models indicated seizure

generation in a ‘centrencephalic’ upper brainstem/thalamic system with diffuse cortical projections. However, intracarotid injections of metrazol as a provocative and amobarbital as an inhibitory agent in patients with suspected secondary bilateral synchrony established a prominent role of the cerebral cortex, unilateral stimulation of which produced a bilateral symmetric response. Gloor [4] concluded that “a fundamental disturbance of the normal interaction between cortex and subcortical projection mechanisms of reticular origin is common to all forms of generalized epilepsies associated with generalized bilaterally synchronous spike and wave discharges”. In its essence, this view became largely accepted by the scientific community. Later experimental work to define details of the pathological circuit was recently reviewed by Avoli [5].

### The seizure types & syndromes

The clinical presentation of generalized epilepsies is varied. Most frequent and best investigated are the seizures and





**Figure 2. 'Generalized' epileptiform discharge.** Rhythmic train of 3 Hz spike-and-slow-wave complexes. The discharges are bilateral and synchronous, but not generalized. There is a clear frontal maximum. The centroparietal discharges are in phase with the frontal ones, while all other channels showed activity that is out-of-phase/opposite polarity compared with the frontal signals. Common average montage (scale: 1 s  $\times$  70  $\mu$ V).

syndromes belonging to the group of idiopathic generalized epilepsies (IGEs), which are genetically determined. Today, juvenile myoclonic epilepsy (JME) is considered the core syndrome of this group where the patients may have three seizure types: myoclonic, absence and GTC. In childhood absence epilepsy with onset in school age and juvenile absence epilepsy with onset in puberty, the presenting seizure type is sudden lapses of consciousness lasting a few seconds where the patients are unresponsive and staring, their movements frozen, often with an upward movement of head and eyeballs. Part of these patients, in addition, have GTCS who may be preceded by a series of absences or myocloni. GTC may also be the only seizure type, typically occurring in the first hour after awakening, in some patients again preceded by absences or myocloni even if they do not have these as independent seizure types.

Absences may include other signs than those above. Rhythmic myocloni mostly of the shoulders and proximal upper extremities, in phase with the SW discharge is considered to constitute a separate syndrome, that is, myoclonic absence epilepsy [6], whereas Jeavons syndrome [7] presents with eyelid myocloni which may or may not be accompanied by absences and is precipitated mainly by eye closure. Individually, absences may habitually comprise focal features like head version, loss of muscle tone or autonomic symptoms; ictal automatisms seem mostly related to absences of prolonged duration.

Along with the three characteristic 'generalized' seizure types of IGE, localized myoclonic seizures are by no means uncommon but underestimated and underreported. They are particularly related to the reflex epileptic traits of JME [8] such

as orofacial reflex myocloni precipitated mainly by reading and talking, and praxis induction [9], whereas myocloni usually occur in the active musculature.

Many of the syndromes in the group of symptomatic or cryptogenic generalized epilepsies [10] are now preferentially described as epileptic encephalopathies [11]. In these, other seizure types are observed like epileptic spasms, tonic and atonic seizures. The absences of these syndromes are considered atypical by less abrupt onset and offset, longer duration, more pronounced changes in muscle tone and more irregular EEG findings [12].

### Reflex epileptic mechanisms & facilitating factors

Reflex epilepsies are defined by seizures, which are habitually, immediately and reproducibly triggered by some qualitatively and sometimes also quantitatively well-defined sensory or cognitive stimulus [13]. Reflex epilepsies were long mostly considered a medical curiosity, but it is now increasingly understood that the well-defined relation between a specific stimulus and a specific epileptic response can provide unique insights into the ictogenesis of human epilepsies. It is thought-provoking that reflex epileptic mechanisms are much more frequent in IGEs than in focal epilepsies. This indicates that IGEs are more likely to respond to exogenous stimuli as a feature of their ictogenesis, which needs an explanation. Of the various subsyndromes of IGE, JME stands out by having four reflex epileptic traits attached to it.

- **Photosensitivity (PhS)** can be found in at least 30% [14] and up to 90% [15] of the patients. PhS has been extensively written about. For details, see Kasteleijn-Nolst *et al.* [16]. Intermittent light stimuli of a critical frequency (mostly from 14 to 30 Hz) after some seconds produce a 'photoparoxysmal response (PPR)' in the EEG (FIGURE 3), that is, SW discharges that are often more prominent on the occipital than the frontal leads [14]. With continuous stimulation, the PPR may more or less rapidly evolve into a clinical seizure. Bilateral myoclonic seizures of the upper extremities are the most frequent provoked seizure type, followed by absences and GTCS or, much more rarely, focal occipital seizures with version of head and eyes and/or visual aura [14]. PhS indicates involvement of the occipital cortex, that is, the stimulated area, in ictogenesis.
- **Praxis induction** is defined as precipitation of seizures by deliberate and targeted movements, typically in a complex visuomotor context involving decision-making (playing of chess and cards, spatial construction, etc.). Matsuoka *et al.* [17] in a systematic study found the trait in half the patients with JME in Japan, whereas it was not quite as frequent in Germany and Brazil [9]. The myocloni manifest in the muscles active in the task.
- **Oro-facial reflex myocloni (ORM)** are small, lightning-like, unilateral or bilateral single myocloni of lips, jaw and throat precipitated by reading and talking. These were first described as the presenting symptom of primary reading

epilepsy [8] but later also identified as a frequent trait of JME [18]. In reading, the precipitating mechanism is unrelated to the contents but quantitatively dependent on the formal difficulty of the task [8]. It involves the bilateral occipital and parietal cortex, the language areas and the motor cortex. After upgrading of this complex cognitive system, myocloni will develop in its periphery in the active musculature. ORM has also been described in response to motor tasks involving the hands [19].

- **Eye closure sensitivity (ECS)** consists of SW discharges with or without clinical seizures appearing within 1–2 s after eye closure. The related seizure type is eyelid myoclonus with or without absence, and the trait is also observed in other syndromes of IGE [20] and in the rare Jeavons syndrome [7] where it is a mandatory feature. Proprioception from the eyelid musculature and myoclonic response in the same indicate action in a brief reflex loop.

In a cohort of 65 JME patients [21] aged  $24.4 \pm 7.28$  years who were systematically tested, including video-EEG documentation, for the presence, at the time of investigation, of these four reflex epileptic traits, only 27 (41%) had none. Sixteen (24.6%) patients were photosensitive, 22 (33.8%) had praxis induction, 17 (26%) ORM and 13 (20%) ECS. The comparatively low figure for PhS is probably explained by noninclusion of historical data and successful treatment. The figure for ECS is unexpectedly high in this study, but probably realistic because here it was systematically tested for the first time.

Unlike rodents, audiogenic as well as other sensory triggers but visual seem to be virtually absent in human generalized epilepsies.

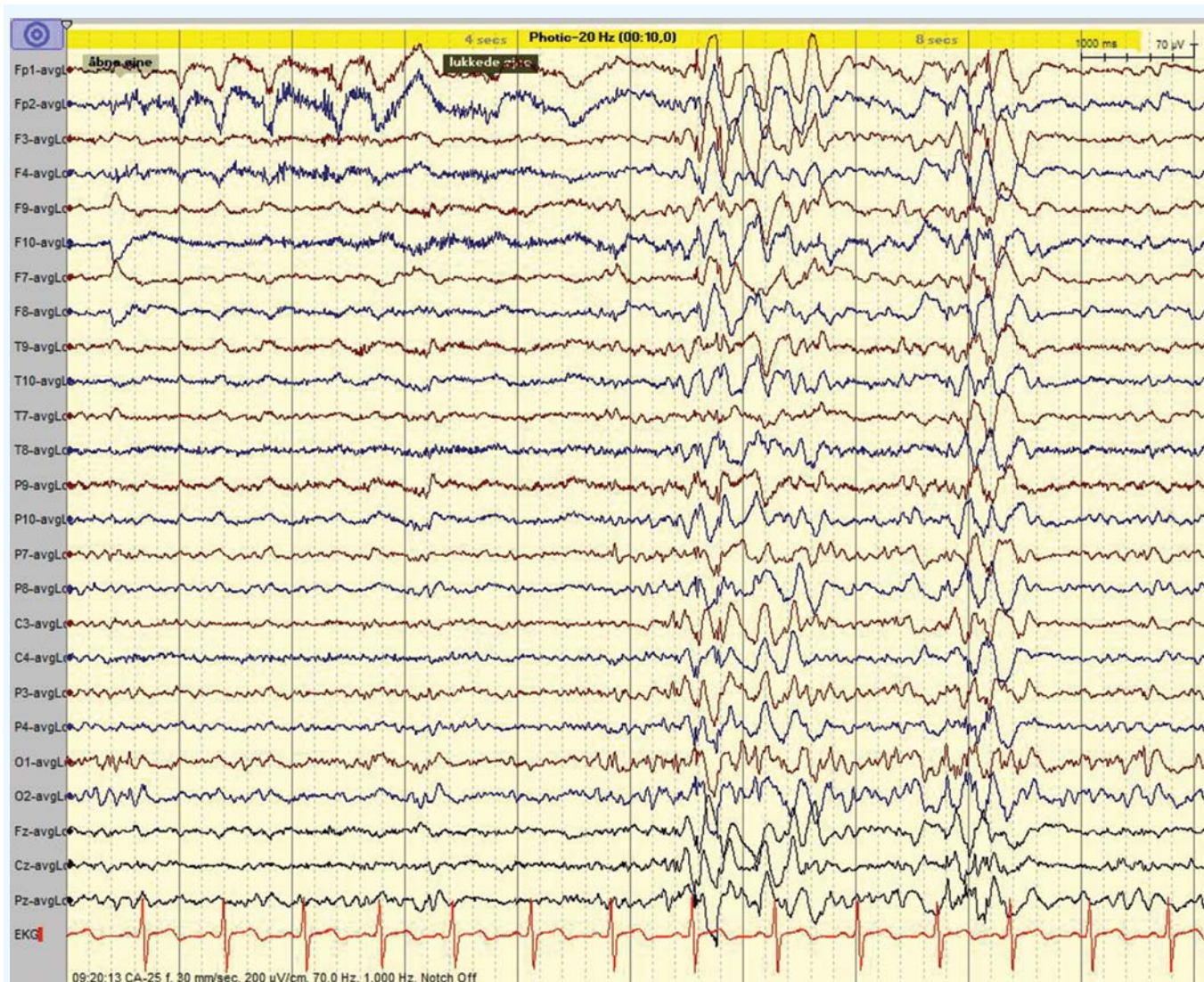
It is important to emphasize that potentially ictogenic cognitive tasks, presumably by increasing attention, may also inhibit the occurrence of epileptiform EEG discharges, thus we talk about a bidirectional modulation (facilitation or inhibition) of the activity in the ictogenic network [19].

### Facilitating factors of seizures in IGEs

The time-honored clinical knowledge that not all seizures are fully spontaneous but may be facilitated by factors like sleep deprivation, excessive alcohol intake or extraordinary stress has been difficult to corroborate by objective studies. The role of sleep deprivation for first seizures in life was confirmed in a cohort study [22]. Systematic investigations of facilitating factors in established epilepsy started with the seminal paper of Aird [23]. Such factors seem to be particularly important in IGEs [24]. At variance with the action of reflex epileptic triggers on specific ictogenic networks, facilitating factors probably work by general modulation of the brain's seizure propensity or the seizure threshold.

In a study of 400 unselected patients with epilepsy, 62% cited at least one factor [25]. Stress was the most frequent factor in temporal lobe epilepsy, whereas in IGE, stress and sleep deprivation were equally important. Of 75 Brazilian JME patients,





**Figure 3. Photoparoxysmal response.** During intermittent photic stimulation at 20 Hz, spikes are triggered in the left occipital region and then in the frontal region. Common average montage (scale: 1 s  $\times$  70  $\mu$ V).

92% reported at least one trigger factor but this included reflex epileptic mechanisms. Stress and sleep deprivation, again, were clearly the most common factors reported by 62 (82.7%) and 58 (77.3%) patients, respectively [26]. Even if the findings have the disadvantage of being based solely on self-reports, all recent studies used standardized questionnaires and semi-structured interviews and concur in their results. Therefore, the role of stress and sleep deprivation as facilitators of seizures in IGE can today be considered reasonably well established.

### Electroencephalography

The EEG signature of generalized epilepsies is the bilateral synchronous and quasi-symmetric SW pattern (FIGURE 2). In IGEs, the SW frequency typically is between 3 and 5 Hz. A slower frequency is indicative of an epileptic encephalopathy, whereas SWs with a higher frequency (6 Hz) are not necessarily a pathological finding. A common variant is the poly-SW

pattern where the slow wave is preceded by >2 spikes; this pattern is suspicious of a diagnosis of JME. In spite of the common nomenclature ‘generalized SW’, the pattern is never really generalized but usually has a clear frontocentral predominance, sometimes sparing the posterior leads (FIGURE 2). Part of the cases, however, present occipital predominance. This distribution was reported more frequently with PhS (FIGURE 3) [14] and ECS [27].

Asymmetries of the interictal SW pattern are by no means uncommon [28], and local spikes can occur, which are sometimes called ‘pseudofocal’. This does not refer to their formal characteristics but to their appearing in the unexpected context of generalized epilepsy. Such findings intraindividually often vary in localization and lateralization, but in some patients, they are persistent.

Interictal findings and ictal EEG of minor seizures are fundamentally the same. The onset of the SW paroxysms not

rarely is focal, but with varying location. A habitual local onset may be found especially in patients with persistent 'pseudofocal' interictal findings. It is tempting to assume but has not yet been studied that such features are related to local trigger zones, which are now often considered a common feature of generalized ictogenesis (see below).

The ictal EEG of myoclonic seizures typically shows the poly-SW pattern which is interictally an optional feature in JME. GTCS in IGE are often preceded by an increase of SW activity which, however, typically disappears a few seconds before the onset of the tonic phase. While the ictal EEG of GTCS is veiled by muscle artifacts, analysis of the ictal EMG has provided important insights into the mechanisms shaping the subsequent phases of these seizures. They indicated an important role already at seizure onset for the inhibitory mechanisms eventually terminating the seizures [29].

Likewise, EMG analysis has demonstrated that the electrophysiological mechanisms underlying the tonic phase of GTCS from the onset differ from tonic seizures. It was hypothesized that the tonic phase of GTCS is mainly due to excessive activation of the corticospinal system, whereas the extrapyramidal system seems to be involved in tonic seizures [30].

The EEG of tonic seizures that are particularly common in Lennox–Gastaut syndrome [31] is characterized by runs of generalized spikes of 10–25 Hz. Atypical absences have a slower SW frequency ( $\leq 2.5$  Hz), fast or other paroxysmal activity, which is more asymmetrical and irregular [12]. The EEGs of epileptic encephalopathies of an earlier age showed suppression-burst patterns [32] or hypsarrhythmia (infantile spasms, [33]) sometimes with low amplitude fast activity at the time of a spasm.

Advanced methods of EEG analysis have been used to identify ictogenic networks in generalized epilepsies. Tucker *et al.* [34] applied source analysis to dense array (256 channel) EEGs of 25 absences of five patients and found neither onset nor spread of the seizures as being 'generalized'. The slow waves were restricted to frontotemporal networks, and the spikes seemed to represent a highly localized and stereotyped progression of activity in ventromedial frontal networks. Lee *et al.* [35] applied direct transfer function to the SW discharges of seven JME patients and ascribed a key role for their generation to the precuneus as part of a network also involving the frontal cortex and the thalamus.

## Other electrophysiological investigations

### Magnetencephalography

Stefan *et al.* [36] using magnetencephalography (MEG) source analysis of SW found involvement of frontal, peri-insular and thalamic areas in seven IGE patients, with central and premotor localizations being mostly involved in patients with myocloni and prefrontal areas in those without. Sakurai *et al.* [37] found default mode network (DMN, medial prefrontal, posterior cingulate and precuneus) activation at absence onset in five patients with juvenile absence epilepsy. Gupta *et al.* [38] looked at the period preceding absences. They described a dynamic

network process building up to an absence and starting in occipital followed by frontal sources. Increase in clustering and decrease in path length were seen preceding the SW onset, and a rhythmic pattern of increasing and decreasing connectivity during SW discharges. Unfortunately, it is not known how many in their small sample of five patients were photosensitive. In photosensitive patients, Parra *et al.* [39] found increased synchronization of  $\gamma$  (30–120 Hz) activity, harmonically related to stimulation frequency, only if a PPR was elicited and preceding it.

### Transcranial magnetic stimulation

Transcranial magnetic stimulation is a suitable method to study cortical excitability, and preliminary findings in IGEs suggest syndrome-specific changes in cortical excitability. In JME, the excitability of the motor cortex is increased, explaining the myoclonic jerks in these patients [40,41]. The hyperexcitability was more pronounced in the morning and after sleep deprivation [42,43], which is consistent with the clinical observations in these patients. An investigation of phosphene threshold in photosensitive patients clearly indicated increased excitability of the primary visual cortex [44]. Intermittent light stimulation in photosensitive patients had only marginal effects on excitability of the pyramidal system [45]. The syndrome-specific excitability changes in the motor cortex (JME) and visual cortex (photosensitive patients) further support the model of system epilepsies.

### Morphological findings

The traditional definition of IGE includes that there are no morphological findings [10]. This, however, is no longer true since microstructural investigations have become available. The histological postmortem findings of Meencke and Janz [46] of cortical microdysgenesis have meantime been supplemented by voxel-based magnetic resonance (MR) morphometric studies. A recent meta-analysis of seven such studies on JME including 211 patients and 241 controls [47] concluded that, whereas some findings were inconsistent, both increased gray matter density in the bilateral medial frontal and anterior cingulate gyri, and decreased gray matter density in the bilateral thalamus come out as robust results.

Another MR-based morphological approach, surface-based morphometry, showed increased cortical thickness in the orbitofrontal and medial frontal cortices coexisting with bilateral reduction in thalamic volume in 24 JME patients compared with 40 healthy controls [48]. Both these subtle morphological findings of an aberrant frontothalamic structure concur with the central role of corticothalamic circuitry in the ictogenesis of JME.

### Functional imaging: single photon emission computerized tomography & PET

Single photon emission computerized tomography (SPECT) in 6 patients with childhood absence epilepsy revealed an overall increase in cerebral blood flow but no local alterations during a



hyperventilation phase comprising several runs of generalized SW of 2–14 s duration, in two cases with clinical absences [49]. Interictal SPECT in 19 JME patients compared with 25 controls showed reduced blood flow in thalamus, brainstem, cerebellum and hippocampus with indications of an increase in the superior frontal and pericentral gyri, suggesting impairment of corticocortical networks [50].

An early study of absences with  $\text{H}_2^{15}\text{O}$  positron emission tomography (PET), [51], provided evidence for an important role of the thalamus, but there was no indication that it was the site of initiation of the seizures.  $^{18}\text{F}$ FDG PET in 19 JME patients demonstrated increased glucose uptake in the thalamus in a 40 min period including some SW activity [52]. However, the SW seemed mostly restricted to the frontal and central leads and lasted from 5.5 to 22.5 s in total, with no clinical seizures recorded. So this is fundamentally an interictal study in spite of the SW activity found.

Beyond such global investigations of metabolism and blood flow, PET with suitable ligands has the potential to reveal deviations of transmitter activities but only few such studies exist. Binding of  $^{11}\text{C}$ -Flumazenil, a marker of  $\text{GABA}_A$  receptors, was found increased in the prefrontal, dorsolateral frontal and, to a lesser extent, the parietal and occipital cortex of five patients with JME [53].

In the same syndrome, a study with  $^{18}\text{F}$ -Fallyprid revealed reduced dopamine receptor binding in the bilateral posterior putamen [54]. Dopamine is assumed to have an inhibitory effect on seizures, and this pathway was also studied, by Ciumas *et al.* [55], with the presynaptic marker  $^{11}\text{C}$  PF21, which binds to the dopamine transporter DAT in 13 patients each with JME and IGE with GTCS only, and 12 healthy controls. In comparison, the DAT binding potential was reduced in both patient groups but in different locations: midbrain in JME and putamen in the GTC patients, with no deviations in the caudate nucleus in either patient groups. The authors concluded that the location of differences in DAT binding in the two patient groups may reflect an involvement of partly diverse neuronal circuits in the two investigated IGE forms.

Serotonin is a transmitter which can be studied with several PET ligands. Meschaks *et al.* [56] investigated 11 JME patients and 11 healthy controls with the serotonin 1A receptor antagonist carbonyl- $^{11}\text{C}$ -WAY-100635. The patients showed reduced binding potential in the dorsolateral prefrontal cortex, raphe nuclei and hippocampus. The authors believed that these findings need to be interpreted with caution, but indicated involvement of the serotonin system in JME and supported that not all brain regions are homogeneously involved in this condition.

### Functional imaging: fMRI

A series of EEG-triggered functional magnetic resonance imaging (fMRI) studies established the involvement of thalamus and DMN in the generation of generalized SW activity. In one study [57], the brainstem reticular structures were involved, and the parietal cortex was suggested as the site of

initiation. An analysis using dynamic causal modeling [58] provided strong evidence that activity in the precuneus gates SW discharges in the thalamo-(frontal) cortical network.

Moeller *et al.* [59] studied the EEG–fMRIs of 17 absences from 9 patients in a sliding window analysis providing a temporal sequence of blood-oxygen level-dependent (BOLD) response maps. Thalamic activation was found in 16 absences (94%), deactivation in DMN areas in 15 (88%), deactivation of the caudate nuclei in 10 (59%) and cortical trigger sites in patient-specific areas in 10 (59%) of the absences (frontal in six patients and paramedian parietal in one). In three patients (33%), no cortical trigger was identified. Cortical activations and deactivations in default mode areas and caudate nucleus occurred significantly earlier than thalamic responses. If a patient had more than one absence, the BOLD signal changes were consistent across different absences.

Benuzzi *et al.* [60] further investigated the dynamics of absence generation by looking at the BOLD signal development in 15 patients with IGE, in 3 s epochs from 18 s before to 18 s after the onset of SW discharges. A total of 262 generalized SW events with a duration of 1–42 s (mean 4 s) were registered. BOLD increments starting approximately 10 s before SW onset were located in frontal and parietal cortical areas, and especially in the precuneus–posterior cingulate region. At SW onset, BOLD increments were located in thalamus, cerebellum and anterior cingulate gyrus. In this phase, BOLD decrements were observed in the DMN persisting until 9 s after onset. The authors proposed two possible hypotheses. The observed early BOLD changes could represent a primary dysfunction of DMN structures in patients with IGE, synchronization of neuronal activity in the DMN regions representing the trigger of seizure occurrence. Alternatively, early BOLD increments could represent the functional correlate of physiological alertness oscillations that are time locked to SW discharges in susceptible brains prone to seizures. It should be noted that these authors like Moeller *et al.* [59] found local cortical onset sites that were variable but subject specific.

At variance with these remarkably consistent findings with spontaneous SW activity in absence patients, the SW of the PPR in photosensitive patients seems to be generated independently from the thalamus. In a study of six photosensitive subjects where a PPR could be registered during fMRI, Moeller *et al.* [61] looked at the BOLD signal 3 s before and at the onset of the SW discharges. At first, five subjects showed activation in the parietal cortex, and all subjects showed activation in the premotor cortex. The global maximum of the PPR-associated BOLD signal increase was found in the parietal cortex adjacent to the intraparietal sulcus in four, and in the frontal cortex in two subjects. At PPR onset, all subjects presented deactivation in areas that had first shown activation. A deactivation of the caudate nucleus was found twice. PPR-related BOLD signal changes in the thalamus were only detected in one subject. The authors concluded that ‘in contrast to spontaneous GSW, these results suggest that PPR is a

cortical phenomenon with an involvement of the parietal and frontal cortices’.

In one patient of this investigation, the PPR evolved into a GTCS, via a visual aura [62], and an increased BOLD signal was found, at the time of the visual hallucination, in the bilateral superior collicles, lateral geniculate bodies and thalamus. Thus, the thalamus got first involved with progression from subclinical SW (the PPR) to a clinical seizure.

Orofacial reflex myocloni precipitated by reading were studied by Salek-Haddadi *et al.* [63] in 9 patients with ORM, six of whom had seizures during fMRI assessment. Ictal activation was compared with activation by motor and language mapping tasks. Ictal BOLD activations were overlapping or adjacent to areas physiologically activated during language and facial motor tasks. Based on these findings, the authors hypothesized that reflex seizures occur in reading epilepsy when a critical mass of neurons is activated through a provoking stimulus within corticoreticular and corticocortical circuitry subserving normal functions.

One of the most important contributions to the understanding of ictogenesis in JME was that of Vollmar *et al.* [64] who investigated visuomotor coordination in 30 patients and 26 healthy controls with a working memory task in which the patients performed as well as the controls but displayed hyperactivation and hyperconnectivity of the primary motor cortex and the supplementary motor area. Furthermore, the concomitant physiological deactivation of the DMN during the task was impaired. They concluded that ‘an ‘overload’ of the task-positive cognitive network during a highly demanding task, together with impaired deactivation of the DMN, could lead to hyperexcitability and hyperconnectivity across systems, including the motor cortex, and cause myoclonic jerks’ [64].

### Generalized ictogenesis & functional anatomy

Many of the newer findings reported above concur in indicating that ictogenic mechanisms in IGEs largely use pre-existing functional anatomical networks that normally serve highly important physiological functions such as the DMN for self-awareness, the network for visuomotor coordination and working memory, and the audio-(visuo-) motor network for interactive language. PhS that is so common in these epilepsies may be an indicator of upregulation of the occipitofrontal long-loop connections as hyperexcitability by upregulation of these CNS subsystems seems to be a key factor. As IGEs have a primarily genetic etiology, it can be hypothesized that these functional impairments express malfunction of a set of neurons with mutated ion channels or synaptic structures. Newer morphological findings, in addition, indicate the existence of subtle anatomical impairments in the structures involved in the ictogenic networks.

A similar ictogenic principle of dysfunction of CNS subsystems affecting immature cortical-subcortical interactions, for example, serving motor performance has been proposed for some symptomatic generalized epilepsies or epileptic encephalopathies. Such mechanisms can explain the rather homogeneous

phenotype of West syndrome where there is a multitude of possible etiologies with a narrow age of onset or state of CNS maturation as the common denominator. For details of this discussion, see Capovilla *et al.* [65].

### Relation of generalized ictogenesis to other epilepsies

Ictogenesis in age-dependent idiopathic localization-related epilepsies such as primary reading epilepsy (PRE) and Benign childhood epilepsy with centrotemporal spikes is probably not fundamentally different from generalized ictogenesis. ORM in JME and PRE are phenotypically identical, and fMRI has been primarily studied in PRE [63]. The ictogenesis of focal motor seizures in Benign childhood epilepsy with centro-temporal spikes is in principle bilateral although not synchronous and appears to originate in the developing sensorimotor system modulated by sleep-regulating mechanisms [66].

In comparison, ictogenesis in focal epilepsies, too, is no longer understood as a strictly local mechanism, but involving networks that are even rather widespread [67]. However, unlike generalized epilepsies, these networks seem to be individual and generated *de novo* rather than syndrome specific and pre-existing, and relating primarily to local pathologies rather than functional anatomy.

### Therapeutic implications

The treatment with antiepileptic drugs (AEDs) is largely empirical, and the new findings reported above have not yet changed that. Even with the new knowledge about ictogenesis of IGEs, the reasons why sodium channel blockers in most cases (but not always) are inefficient or even have a negative therapeutic effect remain poorly understood. Activation of the GABA<sub>A</sub> receptors in the ventrobasal thalamus has been proposed as a possible mechanism [68]. Valproic acid (VPA) has long been considered the drug of first choice but has lost much ground primarily because of side effects. In women of childbearing age, it is now often considered contraindicated because of its well-established elevated teratogenic risks [69]. By many, levetiracetam is today used as first choice in JME, especially regarding the myoclonic seizures. Good effects have also been reported with lamotrigine (LTG), topiramate, zonisamide and lacosamide with the caveat that LTG may provoke myocloni [70]. Recently, excellent long-term effects of primidone alone or in combination with VPA have been reported for JME [71].

In a recent comparative study of three drugs in 453 children with absences [72], LTG was less effective than VPA, whereas calcium channel blocker ethosuximide looked best because of excellent effect and fewer side effects. LTG like other sodium channel blockers is contraindicated in early childhood epilepsies with myoclonic seizures because the latter are often worsened.

The therapeutic response of focal seizures differs according to their syndromatic context. As symptoms of idiopathic localization-related epilepsies, with ictogenic mechanisms similar to IGEs as just discussed, their response to AEDs also is similar, whereas otherwise sodium channel blockers are the drugs of first choice. The present understanding of ictogenesis



is not yet sufficient to explain the broad-spectrum action of such different AEDs as levetiracetam, VPA or Phenobarbital.

The role of local cortical factors in the ictogenesis of generalized  $\geq 3$  Hz SW activity and seizures is now much better understood as triggers of pathological resonance in widely distributed bilateral circuits. The earlier concept of a local pathology with rapid secondary bilateral synchrony, where a neurosurgical approach could be considered [4], has largely been abandoned. Resective neurosurgery as a curative approach has definitely no place in IGEs even if local findings exist. Contrariwise, system epilepsies manifesting in early phases of brain development like West syndrome can be set off by gross local pathologies, and these cases are often surgically remediable [73].

Ketogenic diet and modified Atkins diet have a place as an option in drug refractory cases of generalized epilepsy [74] no less than in other epilepsies.

Lifestyle hygiene relates to avoidance or control of factors facilitating seizure occurrence by reducing seizure threshold or increasing seizure propensity. Of the most common factors, disturbances of the sleep–wake cycle and alcohol intake are easier to control than stress. In 25 patients who did not accept pharmacotherapy, this approach worked best in cases of IGE (6/12 seizure free, [75]).

Reflex epileptic mechanisms when they are well defined may become the target of specific interventions like stimulus avoidance or sensory protection such as attenuation of intermittent light stimuli by dark [76] or particular blue glasses [77].

Patients who habitually experience seizure events where repetitive absences or myoclonic seizures build up to a GTCS have the possibility to interrupt this development by self-administration of a benzodiazepine like diazepam, lorazepam or midazolam by the buccal, nasal or rectal route. If the prodrome of minor seizures habitually lasts 20 min or more, oral clobazam can be used [78].

### Expert commentary

Recent research, especially using advanced neurophysiological methods and functional imaging, has revolutionized our views of generalized ictogenesis. The notion of a more or less complete involvement of the entire brain or at least the quasi-complete cerebral cortex as suggested by generalized SW discharge on the scalp EEG is not tenable any more. It has been replaced by participation of widely distributed but rather selective parts of the frontal, parietal and occipital cortex, the DMN and parts of the thalamus in a resonance circuitry which can be triggered off from variable sites.

Studies of the frequent reflex epileptic mechanisms and complex cognitive performance indicate that the ictogenic mechanisms largely ‘hijack’ [79] pre-existing anatomical networks normally serving important physiological functions. This understanding is central to the arising theory that considers ‘generalized’ epilepsies as system disorders of the brain. The use of established networks of physiological function can explain the high accessibility of these epilepsies to exogenous factors, both precipitating or inhibiting seizure activity.

For the same reason, nonpharmacological treatments seem to be more useful here than in focal epilepsies. However, generalized epilepsies remain the domain of pharmacotherapy. When the details of action of their genetic causes will be better understood, it will be possible to develop more fitting and targeted pharmacological principles than we have today.

### Five-year view

Many more details of generalized ictogenesis can be expected to be clarified within the next 5 years. The generation of bilateral myoclonic seizures, both spontaneous and photically induced, should get visualized with fMRI as well as some other seizure types. More fMRI studies of patients with multiple subclinical and clinical SW discharges will reveal if and to what extent their local triggers are intraindividually constant or variable.

We have probably only seen the beginning of what MEG can contribute, and more interesting findings with this method can be expected.

The potential of PET to provide markers of regional distribution of mutated gene products is far from being exhausted, but the development of suitable new ligands is time-consuming. However, even small progress within the period will be welcome because this may be the best alley to link functional networks with genetic findings.

It is expected that the system epilepsies concept will be further developed with more precise definition of the physiological systems involved including the relations with non-IGEs and idiopathic localization-related epilepsies.

### Definitions

**Convulsion:** A sudden, violent, irregular movement of the body, caused by involuntary contraction of muscles and associated especially with brain disorders such as epilepsy (Oxford Dictionary).

**Epilepsy:** A disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure [80].

**Epileptic seizure:** A transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain [80].

**Epileptogenesis:** The process by which the previously normal brain is functionally altered and biased towards the generation of abnormal electrical activity that subserves chronic seizures [81].

**Ictogenesis:** The mechanisms causing individual seizures to occur [82]; the transition from the interictal state to a seizure [83].

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## Key issues

- The concept of generalized epilepsy as involving the entire brain (or entire cortex) homogeneously is not valid any longer.
- Generalized seizures are generated in an ictogenic network involving parts of the frontal, parietal and occipital cortex, the default mode network and the thalamus. A variety of triggers feed into this circuit.
- This concept is based upon concurrent findings of advanced neurophysiology, multiple methods of functional imaging and magnetic resonance morphometry.
- On the background of genetically mutated neurons generalized, ictogenesis 'hijacks' functional anatomic networks for important physiological functions using them to produce seizures.
- Generalized epilepsies are therefore now understood as system disorders of the brain.

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