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REVIEW ARTICLE

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Summary

Activation of specific cortical territories by sensory stimuli or of less restricted areas of the brain by cognitive stimuli is known to induce apparently generalized seizures in predisposed patients; this is clinically and electroencephalographically distinct from reflex triggering of partial seizures. Photosensitive patients may have seizures when exposed to environmental stimuli producing appropriate flickering light or geometric patterns. Some children with benign myoclonic epilepsy in infancy have seizures triggered by unexpected touch or noise. Seizures induced by thinking have been reported in response to non-verbal higher mental activity such as mental arithmetic. Praxis-induced seizures are triggered by similar mental activities accompanied by the use of the hands. Language-induced seizures are usually triggered by verbal higher mental activity. Functional imaging and other methods have contributed to understanding how these seizures arise. Patients with these generalized reflex seizures appear to have regions of cortical hyperexcitability overlapping or coinciding with areas physiologically activated during specific sensory stimulations and cognitive or motor activities. When these areas receive appropriate afferent volleys and a critical mass of cortex is activated, an epileptic activity is produced that ultimately involves cortico-reticular or cortico-cortical pathways resulting in a generalized or bilateral epileptic event.

Introduction

Generalized epilepsies and syndromes are characterized by seizures in which the first clinical manifestations indicate initial involvement of both hemispheres and EEG is bilateral at the onset (Commission on Classification and Terminology of the International League Against Epilepsy, 1989). Some patients have generalized or bilateral ictal manifestations such as absences, generalized convulsions or bilateral myoclonic jerks when exposed to stimuli classically related to specific cortical sensory territories. These seizures are, however, associated with idiopathic generalized epilepsy (IGE). This review discusses the electroclinical patterns of generalized reflex seizures triggered by apparently local or regional cortical activation by such stimuli. Sensitivity to flickering light or pattern is the most frequently encountered of these. Activation of less restricted brain areas by stimuli such as calculation or reading can also trigger generalized seizures in some patients. Like photosensitive seizures, these have been studied with classical

EEG, structural imaging, neuropsychological methods, PET, functional MRI (fMRI) and evoked potential studies. Studies of such reflex seizures have also added to knowledge of the mechanisms of generalized epilepsy. Clinically focal seizures triggered by startle, eating, music and somatosensory stimuli, which may generalize and which usually reflect symptomatic epilepsy, will not be discussed in this review.

Seizures induced by visual stimuli

Photosensitive patients have seizures when exposed to flicker such as sun shining through trees and discotheque lights, or with apparently more complex stimuli such as television and videogames. Seizures are commonly characterized by subtle eyelid myoclonus with or without impairment of consciousness, symmetric or asymmetric jerks of the arms, massive jerks of the whole body, or absence seizures. With sustained exposure to the stimulus, these can evolve into generalized tonic–clonic seizures, which can also occur without premonitory events. The EEG usually shows a photoparoxysmal response (PPR) with intermittent photic stimulation (IPS) typically between 10 and 30 flashes/s (for reviews see Kasteleijn-Nolst Trenité, 1998; Zifkin and Kasteleijn-Nolst Trenité, 2000). Among the four different types of PPR described by Waltz *et al.* (1992), only a generalized paroxysmal spike or polyspike and wave discharge is accepted as clearly linked to epilepsy. Photosensitivity is age and sex related. The annual incidence of photosensitivity among all new cases of epilepsy is ~2% but rises to 10% in subjects 7–19 years old (Quirk *et al.*, 1995). It is more frequent in girls and women and has an important genetic component with likely autosomal dominant inheritance with reduced penetrance, although no major photosensitivity gene has been identified (Waltz and Stephani, 2000; Stephani *et al.*, 2004). Complex inheritance with interaction of several susceptibility genes and environmental factors cannot be ruled out. Photosensitivity can occur in several different epilepsy syndromes, the most frequent association being with IGE, especially with juvenile myoclonic epilepsy (JME) in which it is reported in 40–90% of patients (Wolf and Goosses, 1986; Appleton *et al.*, 2000). Pure photosensitive epilepsy is characterized by generalized seizures exclusively provoked by flicker and accounts for ~40% of epilepsy in photosensitive patients (Jeavons and Harding, 1975). Photosensitivity is also common in some symptomatic generalized epilepsies such as Unverricht–Lundborg disease, Lafora disease and neuronal ceroid lipofuscinoses. Visual stimuli can also induce focal seizures in patients with cerebral palsy, brain malformations or ischaemic occipital lesions (Guerrini *et al.*, 1994). Some subjects have idiopathic focal photosensitive occipital seizures (Guerrini *et al.*, 1995; Hennessy and Binnie, 2000).

Pattern sensitivity is, after flicker sensitivity, the most common cause of visually induced seizures. It is characterized by generalized convulsions, absences or brief myoclonic attacks provoked by viewing patterns such as escalator steps, striped wallpaper or clothing. Almost all these patients show a PPR to IPS. The most epileptogenic pattern consists of stripes in sharp contrast to the background, arranged geometrically (Wilkins *et al.*, 1980). With such stimulation, from 17 to 55% of photosensitive patients have epileptiform abnormalities (Naquet *et al.*, 1976; Kasteleijn-Nolst Trenité, 1989), but clinical pattern sensitivity is less common, reported in only 6% of subjects by Kasteleijn-Nolst Trenité (1989).

Seizures induced by television and by videogames are closely linked to sensitivity to IPS and to pattern. In the 1990s, electronic screen games became widespread and, although previously known to experts (De Marco and Ghersini, 1985), more reports of triggered seizures were published, attracting public attention (Ferrie *et al.*, 1994). In the notorious 'Pokemon' incident of 1997, 685 Japanese children and adolescents, most of whom had no history of epilepsy, came to hospitals throughout the country with seizures simultaneously triggered by watching a broadcast cartoon (Ishida *et al.*, 1998). These events were tonic–clonic seizures, myoclonic jerks or absences, and subjects can usually be classified as having pure photosensitive epilepsy or a form of IGE as currently understood, similar to patients having seizures triggered by other videogames (Ferrie *et al.*, 1994). The triggered event was reportedly the initial seizure in most subjects in both. These figures do not, however, account for the possibility of earlier subtle triggered myoclonic seizures, the patient only coming to medical attention after a generalized tonic–clonioc seizure in front of the screen. Partial or clearly secondarily generalized seizures are also increasingly recognized (Hennessy and Binnie, 2000) and may have occurred in this group (Zifkin and Kasteleijn-Nolst Trenité, 2001), as also reported in ~30% of cases studied by Ferrie *et al.* (1994). In Europe, patients with videogame-triggered seizures are more likely to be sensitive to IPS at 50 Hz than are photosensitive patients without videogame seizures (Kasteleijn-Nolst Trenité *et al.*, 1999). Although videogame sensitivity is usually not distinct from epileptic photosensitivity, Ferrie *et al.* (1994) found that 30% of patients with IGE sensitive to videogames were not sensitive to IPS. Game play involves factors not applicable to passive television viewing, and non-photosensitive patients may have seizures, apart from chance, induced by non-specific factors such as prolonged play and sleep deprivation, or by specific but non-visual triggers such as thinking, possibly with decision making, and hand movement (Millett *et al.*, 1999) (see below). Treatment involves a combination of preventive and pharmacological measures (for a review see Covanis *et al.*, 2004). Avoidance of the stimulus by looking away or covering one eye, using polarized glasses or alternate eye patching for monocular viewing, wearing coloured glasses, watching television from a distance of at least 2 m, using a remote control to change channels and viewing a 100 Hz television set (see below) are often effective precautions. Discotheques should also be avoided, not only because of the stroboscope but also because alcohol intake, emotional stress and sleep deprivation contribute to lower the seizure threshold. If these precautions are ineffective or impractical, drug treatment is necessary. Valproate (VPA) is the drug of choice,

with 85% of patients becoming seizure free; benzodiazepines such as clobazam or clonazepam and ethosuximide can be given as second choice (Harding and Jeavons, 1994). Newer antiepileptic drugs such as lamotrigine and levetiracetam have reduced PPR in acute studies (Binnie *et al.*, 1986; Kasteleijn-Nolst Trenité *et al.*, 1996) and may also be useful. Antiepileptic medications are often needed into the third decade, but some patients may remain photosensitive even longer (Jeavons, 1984) and serial EEG evaluation with IPS is recommended.

Epileptogenesis and the epileptogenic components of the stimulus

During the 1920s, Clementi (1929) showed the importance of focal occipital hyperexcitability in photosensitivity in experiments using topical strychnine to produce local cortical hyperexcitability: strychninization of canine posterior cortex followed by photic stimulation induced partial occipital seizures with secondary generalization. Strychninization of a smaller area, but over both occipital lobes at the same time, produced the same results as a more extensive unilateral application. Naturally photosensitive baboons (*Papio papio*) have been studied extensively by Naquet and co-workers. When exposed to IPS, these animals have initial myoclonic jerks of the eyelids followed by jerks of the face, neck, trunk, and finally of the entire body, associated with generalized paroxysmal EEG discharges that first appear over the frontorolandic cortex (Killam *et al.*, 1967). Visual evoked potentials (VEPs) (Menini *et al.*, 1970) show striking hyperexcitability of this region, but an important role is played by cortico-cortical visual pathways from occipital lobes: bioccipital resection eliminates the epileptic discharges (Wada *et al.*, 1973). The corpus callosum is the major structure responsible for the synchronization of the discharges: callosal section suppresses the bisynchronization (Naquet *et al.*, 1972) and hemifield stimulation then produces only contralateral discharges (Fukuda *et al.*, 1989). Because of frontorolandic rather than occipital hyperexcitability, this model is thought to be more similar to human photic cortical reflex myoclonus (PCRM) than to human photosensitive epilepsy (Shibasaki and Neshige, 1987; Cracco and Rossini, 1998). Artieda and Obeso (1993) showed that in patients with PCRM, flash stimuli first activate the occipital cortex, where a potential of normal amplitude is generated, and 7–10 ms later the frontal cortex where an abnormal activity is generated, giving rise to generalized myoclonic jerks with rostrocaudal recruitment. Even so, in both humans and animals, occipital primary visual cortex appears necessary to trigger systems for propagation and generalization of electrical activity with associated clinical manifestations.

Screen flicker frequency is of major importance in seizures induced by television and electronic screen games. The typical European television set generates final flicker rates of ∼25 and 50 Hz, often within the range of sensitivity to IPS irrespective of screen content. The risk of seizures is also increased by reduced distance between the subject and the television screen, probably because reduced distance increases the ability to resolve the vibrating line pattern (Wilkins *et al.*, 1979). For 100 Hz sets, commonly recommended for photosensitive patients in Europe, the frequencies perceived are ∼25 and 100 Hz depending on the viewing distance, which for most patients is beyond the photosensitive range at longer viewing distance (Fylan and Harding, 1997). Not all seizures triggered by video screens fit this pattern. Some patients can develop seizures even at a greater distance and viewing a non-interlaced screen. Sensitivity to the field frequency and to screen content is important in these cases: broadcast of some types of flickering images can induce seizures, and regulation prohibits these in some countries including the UK (for a review see Harding and Takahashi, 2004). After the 1997 Pokemon incident, it was found that rapid changes of blue and red colour frames elicit PPR more frequently than monochromatic ones, and that sensitivity to specific sequences of colours at certain frequencies may also play an important role in the generation of seizures (Harding, 1998; Tobimatsu *et al.*, 1999). Human pattern sensitivity has been a fruitful tool for understanding the pathogenesis of reflex seizures. The visual system is grossly normal in these patients. There are no related abnormalities of visual acuity, stereopsis or colour vision. However, with low-frequency stimuli, normal saturation of VEP amplitude at high contrast and the phase advance with increasing contrast fail in these subjects at some frequencies, suggesting impairment of the contrast gain control mechanism normally present at these frequencies, due to cortical occipital hyperexcitability (Porciatti *et al.*, 2000). This could be explained by reduction of GABAergic transmission, as demonstrated in cats in which the contrast gain control was suppressed by local applications of bicuculline (Morrone *et al.*, 1987). Other evoked potential studies suggest that photosensitive patients may have not only occipital cortex hyperexcitability but also diffuse or multifocal hyperexcitability possibly involving cortico-cortical pathways (Broughton *et al.*, 1969; Shibasaki and Neshige, 1987; Artieda and Obeso, 1993). Takahashi (1989) studied sensitivity to red flicker stimuli and flickering patterns, which are more potent for EEG activation than is the usual white flash IPS. He argued that central red flicker stimulation would activate the striate cortex that immediately would transmit to the non-specific diffuse system, while stimulation by a flickering geometric pattern at the periphery would activate both striate and parastriate cortex before transmitting to the non-specific diffuse system. Wilkins (1995), evaluating several lines of evidence, concluded that pattern-sensitive seizures are triggered in the occipital lobe, require activation of a critical amount of cortex and depend on synchronization of neuronal activity to induce a seizure. Since then, fMRI (Hill *et al.*, 1999) and magnetoencephalography (MEG) (Ricci *et al.*, 1990; Parra *et al.*, 2003) also suggest regional occipital cortical hyperexcitability, regional activations and abnormal neuronal synchronization in photosensitive subjects. MEG in photosensitive subjects showed enhancement of phase synchrony in the gamma band (30–120 Hz) preceding those

photic stimulation trials that evolve into PPR compared with trials not followed by PPR and compared with phase synchrony in non-photosensitive controls, possibly reflecting a pathological synchronization of gamma oscillation that mediates the transition to PPR (Parra *et al*., 2003).

Thus animal and human data suggest that photosensitive patients have a predisposition to develop PPR due to hyperexcitability of the visual cortex. Binnie (2004) recently has reviewed mechanisms of photosensitivity in man with respect to activation of generalized seizures. When appropriate stimuli reach the striate and parastriate areas activating a sufficient and critical amount of cortical tissue and inducing synchronization of neuronal activity, an initial local epileptic discharge is produced; the latter would rapidly involve the cortico-reticular or cortico-cortical pathways with propagation from the parieto-occipital areas and a generalized epileptic discharge. This seems especially likely if there is also more diffuse cortical hyperexcitability, as suggested by some evoked potential studies.

Seizures induced by non-verbal cognitive stimuli

Seizures induced by thinking (reviewed in Goossens *et al*., 1990) have been reported in response to higher non-verbal mental activity such as calculation, decision making, or playing chess or similar games. Seizures usually start during adolescence and consist of generalized tonic–clonic convulsions at times preceded by myoclonic jerks (96%), myoclonic jerks with or without absences (76%), and absence seizures with myoclonic jerks in 60%. Spontaneous seizures occur rarely in 76% of patients. The EEG shows generalized epileptic discharges in 68% of patients, spontaneous or induced by hyperventilation. Regional or localized abnormalities, when present, are often over the right hemisphere, usually frontal or parietal. IPS evokes a PPR in 32% of patients. Activation by mathematics or spatial tasks is found in 72%; some false negatives may be due to testing patients receiving antiepileptic drugs. In patients sufficiently tested, neuropsychological evaluation shows regional deficits typically referable to the parietal lobe (Goossens *et al*., 1990) although structural changes have not been shown. Although there seems to be no Mendelian inheritance, the family history is similar to that of patients with IGE (Goossens *et al*., 1990). The clinical pattern also is suggestive of IGE, especially JME or juvenile absence epilepsy, but many reports pre-date the widespread recognition of JME (for a review see Serratosa, 2001). Unlike photosensitive patients, avoiding the triggering stimuli in this condition is not possible, and the majority of these patients have seizures usually controlled by VPA or clonazepam (Goossens *et al*., 1990).

Epileptogenesis and the epileptogenic components of the stimulus

Wilkins *et al*. (1982) stressed the importance of the spatial components of the task in inducing epileptiform abnormalities: complex multiplication and division with remainder were epileptogenic, while addition, subtraction and simple multiplication and division, thought to involve fewer spatial components, were not. Inoue *et al*. (1994) reviewed 79 patients with seizures provoked by higher brain functions and emphasized the role of a motor component in seizure activation. They introduced the term 'praxis-induced epilepsy' for patients whose seizures are provoked by 'contemplating complicated spatial task in a sequential fashion, making a decision and practically responding by using part of the body'. This was also stressed by Matsuoka *et al*. (2000) who studied the effects of higher mental activity on the EEG of 480 Japanese patients with epilepsy, monitored during cognitive tasks. Thirty-eight patients had triggered generalized or bilateral epileptic discharges often associated with bilateral myoclonic jerks or absences. Thirty-six of these 38 patients were classified as having IGE and 22 of the 36 had JME. Cognitive tasks requiring the use of the hands, such as writing, written calculation or spatial construction, were found to be more epileptogenic than higher mental activities not requiring hand movement, such as mental calculation, although some patients were activated by purely cognitive stimuli without any motor component. Hand movements alone such as finger tapping or drawing meaningless lines were ineffective. Thus, thinking in a non-verbal way seems to be an essential triggering element. The motor component is defining in praxis induction but other patients have seizures induced by thinking alone.

Contribution of functional imaging

The important role played by the left inferior parietal lobule in mental calculation has been long known (Henschen, 1919). Functional imaging of calculation in healthy volunteers (Dehaene *et al*., 1999; Stanescu-Cosson *et al*., 2000) and in patients with acquired or genetic brain lesions and dyscalculia (Cohen *et al*., 2000; Molko *et al*., 2003) has extended this concept further. It is believed that different strategies are used for different numeric tasks: exact calculation is language dependent and recruits networks involving the dominant inferior frontal lobe and angular gyrus, while approximate or complex calculation relies on non-verbal visuo-spatial networks of both parietal lobes (Dehaene *et al*., 1999).

Thus for the patient reported by Wilkins *et al*. (1982), who had increasing likelihood of thinking-induced EEG discharges and seizures with increased multiplication and division task difficulty but was not affected by addition or single-digit multiplication, one can argue that unilateral fronto-parietal activation was not an adequate trigger and that bilateral parietal activation was required to recruit a 'critical mass' of cerebral cortex to induce seizures, analogous to that described for pattern-sensitive epilepsy and reminiscent of Clementi's findings with bilateral strychninization.

fMRI studies performed during number comparison with unilateral motor response may model the brain circuits involved in praxis induction, combining thinking and action.

Three fundamental steps were identified and sequentially associated with specific brain areas: visual identification, activating the right fusiform gyrus; magnitude comparison, mainly activating bilateral inferior parietal structures; and response elaboration and execution, activating the sensorimotor, supplementary motor and insular cortices contralateral to the responding hand (Pinel *et al.*, 1999).

Thus, we may suppose that praxis induction must involve more cerebral areas than those sufficient for seizures triggered by arithmetic or spatial problems without motor response. Praxis induction would activate a 'critical mass' of hyperexcitable cortex beyond parietal cortices and beyond the network subsuming spatial thought alone, i.e. the sensorimotor areas, which are also preferentially involved in JME (Wolf *et al.*, 1994; Panayiotopoulos *et al.*, 1994) with which praxis induction and its triggered seizures are closely associated (Matsuoka *et al.*, 2000).

Reading epilepsy

Reading epilepsy (RE) is a rare syndrome characterized by involuntary jaw jerks, often described as stiffness, numbness, tightness, clicking sensation, stammering, etc., that occur only while reading and that may progress to a generalized tonic–clonic seizure if reading continues (for a review see Ramani, 1998). RE is the only reflex epilepsy accepted as a syndrome and is classified among the 'localization-related epilepsies and syndromes' (Commission on Classification and Terminology of the International League Against Epilepsy, 1989), but electroclinical manifestations strongly suggest that this is not completely accurate for many patients. The current proposed diagnostic scheme defines it as a reflex epilepsy syndrome without specifying a generalized or focal subtype (Engel, 2001). Although some patients have lateralized EEG changes, the clinical events are typically bilateral even in these.

Many RE reports are difficult to interpret: EEG data provided are at times insufficient and difficult to compare, activation procedures differ, and there are few video-EEG studies in older reports (Ramani, 1998). Wolf (1992) reviewed 111 patients with RE. The age of onset is usually in adolescence and young adulthood with a slight preponderance in men (62%). Interictal EEG is normal in 80% of patients, spontaneous spike and wave discharges are present in 11% and temporal paroxysmal discharges in 5%. IPS evokes a PPR in ∼9%, in keeping with an IGE syndrome. During reading activation, 77% have epileptiform discharges consisting of short bursts of sharp waves, spikes or spike and wave complexes that are bilateral and symmetrical in 32%, bilateral but asymmetrical in 38% and unilateral or focal in 30%. Lateralization is more frequent to the language-dominant hemisphere (78%), preferentially over the temporo-parietal region (80%).

A strong genetic component characterizes this syndrome: of 69 index patients reported by Wolf, 28 (41%) had a family history of seizures and, of 20 first-degree family members with sufficient information, 11 also had RE.

Some asymptomatic family members have generalized EEG spike and wave activity but there are no familial cases of localization-related epilepsy. Autosomal inheritance with incomplete penetrance overlapping with a genetic background for IGE was proposed for some families (Daly and Forster, 1975). Most patients have seizures well controlled by VPA or clonazepam, and only a few decided to prevent convulsive seizures by stopping reading as soon as seizures begin (Wolf, 1994).

Radhakrishnan *et al.* (1995) investigated 20 patients with RE. They found generalized and symmetric ictal discharges in 15 patients (75%) and asymmetric or unilateral discharges in five (25%) with lateralization to the dominant hemisphere. They suggested that RE be classified among the IGEs with seizures precipitated by specific modes of activation. Koutroumanidis *et al.* (1998) monitored 17 patients with RE. During the triggered myoclonic jerks, eight had bilateral synchronous epileptic discharges. Two patients had alexia or possibly speech arrest as the only ictal manifestation, associated on the EEG with focal abnormalities over the left posterior temporal area. The authors suggested that these patients had a variant form of partial reading epilepsy.

Language-related tasks other than reading can induce seizures. Argumentative talking and writing were also effective in eight patients described by Radhakrishnan *et al.* (1995) and in 14 patients described by Koutroumanidis *et al.* (1998). Wolf (1992) reported that talking was effective in 27% of patients with RE and writing in 11%, with reading being usually the most powerful stimulus; difficult calculations and playing chess or card games were provocative in some patients. Geschwind and Sherwin (1967) described a patient in whom precipitation of seizures by reading was often necessary for subsequent induction of seizures by writing and speaking. Singing and recitation have also been reported to induce seizures (Herskowitz *et al.*, 1984).

Epileptogenesis and the epileptogenic components of the stimulus

The mechanism by which reading precipitates seizures is still obscure. The only common factor seems to be the transformation of the linguistic material from graphemes into language (Wolf, 1992). Other mechanisms have been proposed usually for single cases or small series. A proprioceptive mechanism was emphasized by some authors (Bickford *et al.*, 1956; Stevens, 1957; Baxter and Bailey, 1961; Brooks and Jirauch, 1971; Wolf, 1992) with afferents from either jaw muscles or extra-ocular muscles. In many patients, reading aloud was more activating than silent reading. Some authors stressed the importance of emotional involvement with the text (Critchley *et al.*, 1959/1960) or its comprehension (Kartsounis, 1988). However, material difficult to understand or decipher, such as nonsense text or foreign languages, was found to be more provocative in 32 of the 34 patients reviewed by Wolf (1992) where this point was given attention, suggesting a role for maximal attention or effort in the act of reading rather than

for comprehension. Although attention is obviously necessary for cognitive activation, Wilkins *et al.* (1982) were able to exclude maximal attention as a sufficient trigger for seizures induced by thinking, although effortful tasks presumably activate more cortex. Disruption of fluent reading, such as by nonsense words or unexpected words during a normal sentence, was found to be provocative in some patients (Forster, 1977) but suggested as useful non-drug treatment for others (Wilkins and Lindsay, 1985).

Because these patients often have seizures triggered by different linguistic activities, some authors have proposed a broader category of language-induced seizures, of which RE would be a part (Geschwind and Sherwin, 1967; Lee *et al.*, 1980). Language may be considered as analogous to the non-verbal triggers of seizures induced by thinking, with two separate but mechanistically similar paradigms for seizures induced by verbal and by non-verbal cognitive tasks. These entities should be considered not as exclusive and separate but as the extremes of a continuum. In 32 patients with IGE, Matsuoka *et al.* (2000) found that linguistic activities were effective in inducing epileptic discharges in five patients, non-linguistic activities in seven, and both linguistic and non-linguistic activities in 20. Hasegawa *et al.* (1981) described a patient with epileptiform EEG activity predominating over the dominant hemisphere during writing and over the non-dominant hemisphere with spatial construction.

Contribution of functional imaging

PET and fMRI have been used extensively to localize the cortical regions involved in language processing, especially reading. During cognitive tasks, many brain areas may be activated together, but the basic operations of cognitive analysis are assumed to be localized (Posner *et al.*, 1988). Traditionally, language has been separated into different types of linguistic information including word form, sound structure (phonology) and word meaning (semantics). Although subtle differences in experimental design can influence brain activity during tasks and lead to contrasting results (Price *et al.*, 1994), there is some agreement that visual word form recognition occurs mainly in both occipital lobes, that phonological decoding involves the left hemisphere mostly in the primary auditory cortex and auditory association areas, and that semantic processing occurs in both hemispheres predominantly over the left middle temporal gyrus and left frontal lobe (Posner *et al.*, 1988; Petersen *et al.*, 1990; Booth *et al.*, 2002). However, the neural systems involved are even more complex: one must also consider that attention, concentration and emotion play an important role in reading.

Koepp *et al.* (1998) performed [¹¹C]diprenorphine PET in a patient with RE and found decreased peri-ictal opioid binding in both temporal lobes and the left frontal lobe, regions that had shown PET activation during normal reading. Archer *et al.* (2003) performed spike-triggered fMRI in a patient with reading epilepsy. During activation tasks, spike-related activity was found in the left precentral gyrus and bilaterally in the central sulcus and globus pallidus. Comparison of fMRI activation observed during spiking with that during reading showed overlap in the left posterior dorsolateral prefrontal cortex. This area was shown to be activated during specific cognitive tasks with a working memory component, and evidence for the involvement of this region in RE also comes from a patient who developed RE after removal of a left premotor arteriovenous malformation (Ritaccio *et al.*, 1992).

One can argue that, on the basis of some predisposition to generalized seizures, probably less marked in RE (spontaneous generalized spike and wave activity is rare), these patients would present different areas of hyperexcitability involving cortical regions normally activated during language tasks, especially reading and less often writing and talking (Koutroumanidis *et al.*, 1998). The hyperexcitability could be due to a genetic predisposition (Daly and Forster, 1975) or to an acquired lesion (Lee *et al.*, 1980). These areas remain latent until an appropriate stimulus activates them, giving rise to epileptic activity.

Reflex seizures in patients with benign myoclonic epilepsy in infancy (BMEI)

BMEI is a relatively rare condition classified among the IGEs and characterized by brief myoclonic seizures starting in normal infants between 6 months and 3 years (for a review see Dravet and Bureau, 2002). Some of these children present seizures triggered by unexpected sensory stimulation, such as sudden touch, thermal stimuli or noise. After the first description of six children by Ricci *et al.* (1995), more patients have been reported (Cuvellier *et al.*, 1997; Deonna, 1998; Fernandez-Lorente *et al.*, 1999; Caraballo *et al.*, 2003; Kurian and King, 2003; Zafeiriou *et al.*, 2003). A family history of epilepsy or febrile convulsions is present in 30% of the patients, but no multiple cases of BMEI in the same families have been reported. The seizures consist of an initial blink followed by bilateral myoclonic jerks mostly involving the arms, with flexion of the head, upward deviation of the eyes, and falling with more intense attacks. They can occur singly or in clusters. The interictal EEG is usually normal, but spontaneous generalized epileptiform discharges can be recorded, mostly during sleep. IPS infrequently provokes myoclonic jerks. The ictal EEG consists of typical bursts of generalized spike or polyspike and wave discharges at 3 Hz or faster, with frontocentral predominance. Seizures often respond well to valproate and disappear within several months.

Some authors (Ricci *et al.*, 1995) suggest the name 'reflex myoclonic epilepsy in infancy' (RMEI) for patients who have only reflex seizures. Compared with BMEI patients, these children have a shorter duration of disease, only rarely have spontaneous seizures and usually do not have drop attacks.

Epileptogenesis and the epileptogenic components of the stimulus

Little is known about the pathogenesis of RMEI. Cutaneous stimulation can induce partial seizures in patients with localized lesions in the postcentral gyrus (for a review see

Vignal *et al.*, 1998). Sudden sensory stimuli, especially noise, are commonly involved in the precipitation of abnormal startle responses and startle epilepsy (SE). Both partial seizures induced by somatosensory stimulation and SE are clinically and electroencephalographically different from RMEI and typically represent symptomatic epilepsies which do not remit (for a review see Andermann and Andermann, 1986). Although mechanisms of SE are not completely understood, it is believed that the seizures originate in the motor and premotor cortex including the supplementary motor area (Chauvel *et al.*, 1992). An exaggerated startle response, possibly due to abnormal activity in the nucleus reticularis pontis caudalis, would lead to an increase of proprioceptive feedback to the hyperexcitable motor cortex, evoking a seizure (Bancaud *et al.*, 1975).

In RMEI, as in a startle reaction, seizures usually begin with eye blinking and can show a cranio-caudal progression. Moreover, if sudden stimuli are given during a post-myoclonic refractory period, the EEG shows a negative vertex wave, suggesting hyperactivity of the cortex in response to excessive feedback to the initial startle response (Brown *et al.*, 1991; Ricci *et al.*, 1995). An age-dependent, idiopathic disorder characterized by hyperexcitability of the sensorimotor cortex along with an abnormal startle response may be suspected in these patients. These children appear to have an underlying very early-onset IGE; these cases may be analogous to some patients sensitive to startle who have EEG patterns of a symptomatic generalized epilepsy, usually children with diffuse cerebral damage as described by Aguglia *et al.* (1984).

Differentiation from focal reflex seizures and epilepsies

Generalized reflex seizures discussed in this review should be distinguished from focal reflex seizures precipitated by startle (see above), eating, music and somatosensory stimuli. Such patients do not have an IGE and usually have symptomatic focal epilepsies. Eating epilepsy is usually symptomatic, and patients considered to have IGE are exceptional (reviewed in Rémillard *et al.*, 1998). Seizures usually begin in temporo-limbic or extratemporal perisylvian regions and may become secondarily generalized. Musicogenic seizures similarly are focal, and usually symptomatic or cryptogenic, and temporal (reviewed by Zifkin and Zatorre, 1998). Somatosensory stimuli can rarely induce partial seizures in patients with a cerebral lesion. Stimuli such as touch, tapping or rubbing a specific body region, or tooth-brushing may induce focal seizures which may generalize. Proprioceptive stimuli can induce focal seizures in subjects with brain lesions and some acute encephalopathies, especially non-ketotic hyperglycaemia. Hot water epilepsy is usually symptomatic or cryptogenic, and seizures are usually partial.

Discussion

The reflex seizures considered here share many common features of IGE such as age at onset, bilateral myoclonus,

generalized tonic–clonic convulsions and other seizure types associated with IGE such as absences, and symmetric or asymmetric bisynchronous epileptiform EEG discharges. Similarly, they also respond to VPA. Experiments in animals and clinical studies in patients with IGE show that a major role is played by diffuse cortical hyperexcitability responding to normal afferent volleys in the generation of generalized spike and wave discharges (Gloor, 1979; Avoli and Gloor, 1994). As discussed by Wolf *et al.* (1994) and Binnie (1990, 2004), there is no reason to suppose or to require that diffuse cortical hyperexcitability is spatially and temporally uniform and, apart from data gleaned from reflex seizures and photosensitivity, there is evidence that cortical hyperexcitability is not uniform and may differ in degree and extent. Patients with JME can present asymmetrical clinical manifestations and the EEG can show focal interictal discharges as well as asymmetrical discharge onsets (Panayiotopoulos *et al.*, 1991; Aliberti *et al.*, 1994; Lancman *et al.*, 1994). Wolf also emphasized the typical regional predominance of the ictal EEG activity recorded with the myoclonic jerks, themselves more suggestive of rolandic rather than generalized cortical discharge. Taylor *et al.* (2004) documented previously unrecognized focal clinical and EEG occipital features in JME and suggested that there may be genetic determinants shared between JME and idiopathic photosensitive occipital epilepsy, a recognized focal epilepsy syndrome. A neuropathological study (Meencke and Janz, 1984) showed that seven of eight patients with IGE had multiple foci of microdysgenesis, but the interpretation of this is controversial (Lyon and Gastaut, 1985), and Opeskin *et al.* (2000) found no changes in two cases, one with definite and one with probable JME. JME is, however, both clinically and genetically heterogeneous. Advanced neuroimaging studies in patients with IGE showed significantly larger cortical grey matter volumes with increased cortical/subcortical volume ratio compared with controls, postulated to be related to abnormalities in neuronal connectivity (Woermann *et al.*, 1998). The same authors also found an increase in cortical grey matter in mesial frontal lobes in many patients with JME, supporting the concept of focal or regional structural changes associated with abnormalities of functional connectivity in these patients (Woermann *et al.*, 1999). PET may show localized metabolic abnormalities in the mesial frontal region in IGE (Koepp and Duncan, 2000). MR spectroscopy studies showed a reduced concentration of *N*-acetyl aspartate in the mesiofrontal cortex of some JME patients, different from that seen in generalized tonic–clonic seizure patients without JME, suggesting a syndrome-related frontal lobe dysfunction (Savic *et al.*, 2000). Suzuki *et al.* (2004) suggest that mutations in the *EFHC1* gene linked to JME in some subjects may cause increased regional neuron density and produce hyperexcitable neuronal circuits. The EEG pattern and other neurophysiological studies including those of patients with reflex seizures induced by thinking, writing or 'action-programming' suggest a variable focal or regional frontal hyperexcitability in many cases. Even so, although subtle frontal morphological

Table 1 *Regions and systems activated by stimuli triggering generalized reflex seizures*

Generalized reflex seizures	Typical effective stimulus	Regions or systems subserving the trigger
Sensitivity to visual stimuli		
(i) Photosensitivity	Environmental flicker, screen content	Occipital cortex
(ii) Pattern sensitivity	Striped patterns, screen content	Occipital cortex
Sensitivity to other sensory stimuli	Sudden touch or noise	Sensorimotor cortex (?)
Sensitivity to non-verbal cognitive stimuli		
(i) Thinking induction	Mental arithmetic, Brooks letter task, action-programming	Non-dominant parietal lobe or biparietal networks for non-verbal visuo-spatial thought
(ii) Praxis induction	Block design	Non-dominant parietal lobe or biparietal networks for non-verbal visuo-spatial thought, and rolandic areas
Sensitivity to verbal cognitive stimuli	Reading, talking, writing	Both hemispheres predominantly dominant fronto-temporal lobes

changes can be found, they are not universal in JME, and neither is sensitivity to various cognitive triggers which may be absent in a typical case or present in a patient with another IGE syndrome. The association with photosensitivity is also variable. There is also much genetic heterogeneity in JME. Evidence from reflex seizures, summarized by Binnie (2004), and from such studies suggests that the nosologic purity of JME, and of IGE more broadly considered, must be questioned. A purely syndromic approach may be contrasted with the proposed neurobiological continuum of epilepsies discussed by Berkovic *et al.* (1994). It could be hypothesized that those patients with cortical triggers of generalized or bilateral reflex seizures present regions of cortical hyperexcitability overlapping or coinciding with the areas physiologically activated during sensory stimulations (flash, pattern, sudden touch or noise) and cognitive (thinking or reading) or planned motor (praxis) activities. These hyperexcitable regions may be topographically distributed involving contiguous cortex, or follow the localization of the cortical networks subserving specific functions. In the case of sensitivity to flicker or to pattern, the relevant hyperexcitable system is localized to occipital lobes, but other cortical functions are not localized to such relatively small cortical territories. Patients with RMEI may have hyperexcitability of the sensorimotor cortex along with an abnormal startle response. For verbal and non-verbal cognitive tasks, the relevant systems involve complex networks extending over multiple cortical areas in both hemispheres. Depending on the degree and the extent of the network hyperexcitability, the cumulative effect of different factors may be necessary to provoke a seizure. When these hyperexcitable areas receive appropriate afferent volleys and a critical mass of cortex is activated, epileptic activity is produced that ultimately involves the cortico-reticular or cortico-cortical pathways, with the final result of a generalized or bilateral epileptic event. The hyperexcitability could be due to a genetic predisposition or to an acquired lesion superimposed on a genetic trait for IGE. One can argue that in some of these patients, disordered neuronal fine structure or connectivity, or regional alterations in

inhibition could be the cause of the cortical hyperexcitability as discussed by Palmini *et al.* (1995) and by Preul *et al.* (1997), and as suggested by some genetic studies of IGE and JME (Haug *et al.*, 2003; Pal *et al.*, 2003; Gallagher *et al.*, 2004; Suzuki *et al.*, 2004).

In conclusion, we believe that four major patterns of generalized or bilateral reflex seizures with a focal cortical trigger can be identified (see Table 1). Some overlap can exist among the different forms. The underlying mechanisms are similar, as are the resulting seizure types, but the triggers are different and the nature of the effective triggers depends on the distribution of cortical hyperexcitability which can be diffuse but not necessarily uniform. Many such patients appear clinically to have an IGE, especially JME, and the existence of different stimuli triggering these seizures is additional evidence that the cortical mechanisms of IGE are complex and non-uniform.

Acknowledgements

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