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Pathophysiology of Epileptic Encephalopathies

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Summary

The application of metabolic imaging, genetic analysis, and now the development of appropriate animal models has generated critical insights into the pathogenesis of epileptic encephalopathies. In this chapter we have presented ideas intended to move from the lesions associated with epileptic encephalopathies towards understanding the effects of these lesions on the functioning of the brain, specifically of the cortex. We have argued that the effects of focal lesions may be magnified through the interaction between cortical and subcortical structures, and that disruption of subcortical arousal centers regulating cortex early in life may lead to alterations of intracortical synapses that affect a critical period of cognitive development. Impairment of interneuronal function globally through the action of a genetic lesion, similarly causes widespread cortical dysfunction manifesting as increase delta slow waves on EEG and as developmental delay or arrest clinically. Finally, prolonged focal epileptic activity during sleep (as occurring in ESES) might interfere with local SWA at the site of the epileptic focus, impairing the neural processes and, possibly, the local plastic changes associated with learning and other cognitive functions. Seizures may certainly add to these pathological processes, but are likely not necessary for the development of the cognitive pathology. Nevertheless, while seizures, may be either a consequence or symptom of the underlying lesion, their effective treatment can improve outcomes as both clinical and experimental studies may suggest. Understanding their substrates may lead to novel, effective treatments for all aspects of the epileptic encephalopathy phenotype.

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Keywords

epileptic encephalopathy; epilepsy; mental retardation; cognitive impairment; interneuron; genetics; subcortical nuclei; synapse; synaptic plasticity; animal models

Introduction

Understanding the pathophysiology of epileptic encephalopathies has benefitted significantly from advances in functional imaging, primarily with PET and fMRI, in genetics, with identification of specific genes implicated in pathogenesis, such SCN1a, ARX, and CNTNAP, and in development of animal models. Each of these lines of investigation has developed novel and intriguing hypotheses, but a unifying theory of the cause of epileptic encephalopathies remains elusive. The process of synthesizing multiple lines of evidence into hypotheses nevertheless is an essential step to frame further discussion and highlight new questions amenable to experimental investigation.

The International League Against Epilepsy (ILAE 2010) has defined epileptic encephalopathies as:

> "the notion that the epileptic activity itself may contribute to severe cognitive and behavioral impairments above and beyond what might be expected from the underlying pathology alone (e.g., cortical malformation), and that these can worsen over time. These impairments may be global or more selective and they may occur along a spectrum of severity. Although certain syndromes are often referred to as epileptic encephalopathies, the encephalopathic effects of seizures and epilepsy may potentially occur in association with any form of epilepsy. …"

However, the same document goes on to note:

> "… We must, however, recognize that the source of an apparent encephalopathy is usually unknown. It may be the product of the underlying cause, the result of epileptic process, or a combination of both."

In this review, the authors consider several questions central to understanding the pathophysiology of epileptic encephalopathies. First, what is the central derangement present in these disorders, indeed, is there a single, few or many different mechanisms resulting in the spectrum of clinical phenotypes? Are seizures, central to development of encephalopathy? Without doubt seizures are often prominent. Frequent seizures, however, may be present in patients without significant cognitive impairment. What is more, severe encephalopathy may occur out of proportion to the frequency of seizure as in Landau Kleffner syndrome, and may cause greater disability than seizures alone. Is there an additive effect of seizures on encephalopathy? The effects of epileptic activity on cortical function and cognitive processing have been the focus of a number of investigators (Kleen et al., 2012; Henderson et al 2011; Lado et al., 2002), however it is the thesis of the authors that the magnitude of cognitive effects resulting from experimentally induced seizures in animals is significantly smaller than the cognitive devastation seen in the syndromes comprising epileptic encephalopathies. Are the seizures a marker of a more subtly developing encephalopathy and thus the precipitating event that bring the subject to medical attention? Finally, what is the role of subclinical seizures or a significant epileptiform EEG which can be continuous as in hypsarrhythmia or ESES or occasional as in Landau Kleffner with an intermittent form in BRE (with varying degrees of cognitive impairment).

Pathological processes impairing cognition globally may either localize diffusely or multifocally throughout cortex, for example in the form of abnormal cortical neuronal

function, or centrally, in subcortical regions regulating cortical input, output, and tone, such as the thalamus and rostral brainstem. Focal epileptic discharges have the potential to alter cortical function, affecting specific cognitive functions. In animal models (Kleen et al., 2012; Henderson et al., 2011), and likely humans (Lado et al., 2002), seizures and interictal discharges cause synaptic changes that interfere with normal cortical function and learning. The presence of an epileptic focus can alter the metabolism in the affected and connected regions, indicating a widespread effect of focal epilepsy on brain functioning. The alteration of metabolism in epileptic tissue, as visualized with FDG-PET (Kumar et al., 2012), and with MRI spectroscopy (Pan et al., 2008), may also show reversible functional impairment that resolves when seizures are controlled. Memory complaints, presumably due either to a loss of hippocampal neurons or to synaptic rearrangement in the dentate, are frequently associated with temporal lobe epilepsy. However, the presence of seizures alone, even very frequent seizures, does not invariably produce cognitive impairment.

If present at all, the cognitive impairments associated with childhood and juvenile absence epilepsy, or with some forms of frontal lobe epilepsy with frequent nocturnal seizures–are mild, often only appreciated with psychometric testing. In contrast, the seizures associated with epileptic encephalopathies – such as West Syndrome or Lennox-Gastaut Syndrome, are typically brief, produce transient changes in the EEG, and occur for only a relatively brief proportion of each day, and yet are associated with a catastrophic failure of cognitive development. What then is the relationship between the epileptic changes and the encephalopathy? Undoubtedly, the answer varies with the specific syndrome. Nevertheless, some mechanisms of encephalopathy may be shared. It is reasonable to speculate that for syndromes in which the encephalopathy – Dravet, West Syndrome or Lennox-Gastaut Syndrome - is significantly more prominent, that both epilepsy and encephalopathy are the outcome of a common occult etiology, but are not themselves causally related. In syndromes in which impairments of cognitive function are focal or mild and occur relatively late in development, and in which the frequency of epileptic spiking may be high, such as continuous spike wave in slow sleep (CSWSS), one may conceive of a causal relationship between epileptic activity and focal cognitive impairment as a result of the disruption of normal cortical processing and possibly alteration of synaptic connections. To be sure, underlying neuronal dysfunction may also be responsible, but an antecedent history of normal development, and the comparatively milder phenotype of cognitive deficits – compared to early life epileptic encephalopathies - suggest that impaired neuronal function is acquired and rests on a relatively normal underlying physiology.

In this review, we consider whether the encephalopathy seen with catastrophic epilepsies arises from the inappropriate regulation of cortical tone – which may be understood as a failure to fully transition the thalamocortical system from an asleep to awake states - or from abnormalities diffusely present within the cortex – particularly in the interneuronal elements – that both increase epileptogenicity while disrupting intracortical networks, or from a combination of these mechanisms. Indeed, the cortical and subcortical mechanisms may interact in the immature brain, with the cortical abnormality altering subcortical function, which in turn, results in widespread functional change in otherwise normal cortex. The abnormal cortical-subcortical-cortical circuits have been proposed as mechanism contributing to West syndrome. (Lado et al., 2002; Chugani, 2002). These hypothesized mechanisms draw support from the observation that resections of focal cortical abnormalities in children with West Syndrome can lead to resolution of West syndrome and resumption of normal development. (Chugani et al., 1990). Non-invasive imaging suggests that in epileptic encephalopathies there may be focal regions of hypermetabolism associated with widespread regions of hypometabolism that normalize if the encephalopathy resolves lending support to the notion that both cortical and diffusely projecting subcortical mechanisms are involved. (De Tiège et al., 2008; De Tiàge et al., 2009). The development of

two animal models of West syndrome, the multi-hit model and the tetradoxin model offer a means to test these hypotheses. (Swann & Moshe, 2012; Galanopoulou, 2013). The pathophysiology of epileptic encephalopathies, then involves cortical and subcortical regions, and derives from the following elements:

1. A region of abnormal irritable epileptogenic cortex – that may be focal as in the case of focal cortical dysplasias, or widespread as in the case of genetic lesions.
2. Altered function in subcortical regions – cholinergic, serotonergic, and catecholaminergic – that received cortical outflow and in turn regulate cortical input and tone.
3. Diffuse cortical hypoactivity resulting from (2)
4. Encephalopathy is the effect of either (1) or (3), or both.

Encephalopathy arising from cortical interneuronal dysfunction

A number of genetic lesions associated with early life epileptic encephalopathies offer a mechanism that affects cortical function diffusely. The SCN1a mutation may be considered an emerging archetype of a genetic lesions resulting in an epileptic encephalopathy. The association of SCN1a gene mutations with Dravet syndrome and with generalized epilepsy with febrile seizures plus (GEFS+), and subsequently with a wide array of epilepsy phenotypes, provides a possible window on understanding the interplay of neuronal populations in cortex and where changes in membrane properties of one neuronal population create an epilepsy phenotype and likely produce diffuse cortical dysfunction. The SCN1a mutations are a heterogeneous group of loss of function mutations in voltage gated sodium channels. While this would seemingly predispose to decreased neuronal activity, the *in vivo* effect is an increase in epileptogenicity. In fact, hippocampal pyramidal neurons of SCN1a heterozygous or homozygous mice show normal sodium currents unaltered by the presence of the SCN1a mutation. The same mice, however, manifest a marked reduction of sodium currents in the inhibitory interneurons present in hippocampus, leading to the hypothesis that the epileptogenic effects of the SCN1a mutation are mediated by changes in the behavior of inhibitory interneurons in the cortex. (Catterall et al., 2010) Dutton and colleagues (Dutton et al., 2013) have further investigated the effects of the SCN1a mutation by using conditional knock-out of SCN1a selectively in either whole brain, only inhibitory interneurons, or only excitatory pyramidal cells. In normal mice, the SCN1a gene product, Na(v)1.1, was present in 69% of parvalbumin positive GABAergic interneurons. Whereas, only 13% of hippocampal and 5% of neocortical excitatory cells expressed Na(v)1.1. Reduced expression of Na(v)1.1 in interneurons was associated with a decreased seizure threshold when exposed to flurothyl, a chemoconvulsant. Moreover, mice lacking Na(v)1.1 in cortical interneurons developed spontaneous seizures. In contrast, mice lacking Na(v)1.1 selectively in only excitatory cells showed no change in seizure threshold to flurothyl nor had spontaneous seizures.

In addition to seizures, the SCN1a mutation can alter behavior in a manner suggestive of autism. Han and colleagues (Han et al., 2012) observed that mice heterozygous for the SCN1a mutation show autistic-like behaviors, including anxiety, hyperactivity, and stereotyped actions, and decreased social behavior. Homozygosity for the SCN1a mutation was lethal on day 1 of life. Administration of clonazepam, which augments the action of GABA by increasing the conductance of GABA-A channels, rescued the autistic phenotype. The dose of clonazepam used was selected to not cause sedation, and was approximately 20-fold lower than the typical anxiolytic doses.

Aristaless-related homeobox X-linked gene (ARX) mutations are associated with epileptic encephalopathy in early infancy and results histologically in a reduction of interneurons in cortex. The ARX gene codes for a transcription factor important in early cortical development and possibly specific to interneurons. The ARX mutation effects differ depending on whether the lesion is a conditional knock-out deletion or a GCG – polyalanine triplet repeat knock in mutation. The triplet repeat expansion has been found in rare cases of X-linked West syndrome and Ohtahara syndrome, and replicates in mice many of the features associated with the human illness. (Poirier et al., 2008., Kato et al 2003).

The conditional knock-out model – the null mutation is lethal – shows reduction of cortical interneurons, and early life seizures, though not spasms. Adult mice show spasm-like events. (Marsh et al., 2009). A knock-in mouse model that contains the polyalanine expansion seen in human cases manifests spontaneous seizures, including tonic seizures, and autistic behavioral features. Histologically, cortex from these mice shows a 1/3 reduction of GABAergic interneurons staining for calbindin, and preservation of parvalbumin and NPY containing interneurons. Within striatum, on the other hand, there is a reduction NPY and cholinergic interneurons (Price et al., 2009).

Encephalopathy arising from focal cortical dysplasia

Fu and colleagues (Fu et al., 2012) were intrigued by the efficacy of vigabatrin – an enhancer of GABAergic transmission – in the treatment of West syndrome occurring as a result of tuberous sclerosis. These researchers investigated the role of the TSC1 gene mutation – which causes dysregulation of the mTOR pathway, which in turn affects cell growth and protein translation – on the formation of inhibitory interneurons in cortex. In mice with a conditional knock-out of the TSC1 gene, so that only interneurons were affected, there were fewer GABAergic interneurons in the neocortex (20% reduction) and in the hippocampus (25% reduction in CA1, 50% in dentate gyrus). Though the brain appeared grossly normal, the remaining interneurons were enlarged and further assays showed increased signaling in mTORC1 branch of the mTOR pathway in the GABAergic interneurons. Mice with the TSC1 conditional knock-out had increased mortality in early life and had a lower seizure threshold than controls, but did not manifest spontaneous seizures.

Cortical interneurons may also play an critical role in epileptic encephalopathies resulting from focal cortical dysplasia – as in tuberous sclerosis or focal cortical dysplasia implicated in the genesis of West syndrome. (Chugani, 2002; Curatolo et al., 2001). Due in part to the insights gained from understanding the SCN1a mutation where the interaction between genetics and physiology in increasingly understood, and as a result of converging interest the physiology of cortical processing (Levitt et al., 2004), the role of cortical interneurons in epilepsy has been a focus of increased attention. Within cortex, there are multiple GABAergic interneuronal subtypes that may be differentiated from each other histochemically or physiologically. Some interneurons, for example, contain parvalbumin while others contain somatostatin, or neuropeptide Y, or other markers. Similarly, interneurons may be distinguished electrophysiologically by distinct firing behaviors, such as fast-spiking (FS), for example, or low-threshold spiking (LTS) or bursting. GABAergic interneurons of one subtype are frequently interconnected through dendritic gap junctions, increasing the synchronization of firing among the local population of similar interneurons. (Hestrin and Galaretta, 2005). In brain slices, parvalbumin-containing fast-spiking interneurons may play the primary role inhibiting pyramidal cells firing during a seizure discharge (Cammarota et al., 2013), and failure of this interneuronal population can lead to unopposed spread of seizure activity. Sakakibara and colleagues (2012) examined tissue from four patients aged 1–13 years at time of surgery diagnosed with intractable epilepsy beginning in the first year of life and with focal cortical dysplasia visible on imaging. Each

of these patients underwent an extensive resection, including a portion caudate nucleus that contained evidence of dysplastic tissue. In each case there was marked loss of GABAergic interneurons in cortex accompanied by an increased number of GABAergic interneurons in the caudate. Though not characterized as epileptic encephalopathies, the two older children, ages 5y and 13y, had IQ of 59 and 43, respectively. One younger child age 1yr had a DQ of 91, and the youngest child of 3 mo. had not been tested. Inoue and colleagues (Inoue et al., 2013) have reported a case of severe progressive early-onset epileptic encephalopathy characterized by loss of inhibitory interneurons and decreased GABA receptor binding in cortex, among other changes. Animal models of cortical dysplasia have also shown reductions of inhibitory interneuron numbers. Akakin and colleagues (2012) found both parvalbumin-containing and somatostatin-containing interneurons were reduced in newborn rats with focal cortical dysplasia following exposure to intrauterine radiation. Similar results were reported by Takano (2012) who produced examined areas of polymicrogyria in neonatal hamsters injected intracortically with ibotenic acid which causes excitotoxic cell death and a resulting dysplasia. Parvalbumin containing interneurons were significantly reduced in and around the area of polymicrogyria.

Encephalopathy arising from other genetic lesions

In addition to SCN1a deletions, a number of other gene mutations have also been associated with epileptic encephalopathies, particularly those occurring early in life. Even more genes have been associated with autism spectrum disorders (ASD) (Mastrangelo & Leuzzi, 2012). The high prevalence of autistic behaviors in children with epileptic encephalopathies raises the question whether common mechanisms – and possibly common genes - underlie some aspects of ASD and mechanisms contributing to epileptic encephalopathies. Most of the genes associated with epileptic encephalopathy and with ASD, however, are still only associations where the link between genetics and physiology has yet to be unraveled. The ARX gene, discussed earlier, has been linked to ASD. The CNTNAP2 gene is strongly implicated in a small percentage of children with ASD and increases risk of seizures. A recessive mutation in CNTNAP2 causes a syndrome of cortical dysplasia focal epilepsy syndrome in which two-thirds of children are also autistic (Peñagarikano et al., 2011). Linkage analysis has shown that this gene increases the risk of ASD (Arking et al., 2008; Alarcon et al., 2008). A homozygous knockout mouse model showed autistic behaviors, hyperactivity and spontaneous seizures. Histological examination showed overall 20% reduction of GABAergic interneurons in cortex, and a reduction of approximately 10%, 20% and 25% in NPY, calbindin and parvalbumin containing interneurons respectively. There was also a 20–25% reduction in parvalbumin and NPY interneurons in the striatum.

MECP2, the gene responsible for Rett syndrome and one of the first genes to be linked to ASD, is also associated with seizures, though these seizure with Rett syndrome typically occur later in life (Roopra et al., 2012). This variable timing between the onset of encephalopathy and of epilepsy seen across different genetic lesions argues that the encephalopathy and seizures are each products of the gene defect occurring independently rather than one being the consequence of the other.

Encephalopathy arising from abnormal subcortical regulation of cortex

Evidence of the role of subcortical stuctures in the genesis of West syndrome – where this topic has been most studied compared to other epileptic encephalopathies- has been the focus of earlier reviews (Lado & Moshe, 2002 and has been advanced significantly by the PET imaging data from Chugani and colleagues. The question is how changes in subcortical structures can profoundly affect the functioning of even normal cortex. Characteristic findings in patients with epileptic encephalopathies are marked slowing of the EEG

background with multifocal spikes, and either generalized or focal seizures. Of these abnormalities, seizures may be the most dramatic, but marked background slowing of the EEG is the most pervasive and may be the most disruptive to normal cortical processes of learning and development. In the normal brain, slow voltage fluctuations in the range of 1Hz or slower are normally seen in slow-wave sleep. Slow-wave sleep in the normal brain, is the macroscopic phenomena of accompanying periods of neuronal hyperpolarization and silencing of action potentials alternating with brief periods of neuronal activation. These alternating states, termed DOWN and UP states, respectively, are present in neurons within the cortex and within the relay and reticular neurons of the thalamus. It has been suggested that DOWN states play an important role in "renormalizing" stabilizing synaptic connections that are progressively strengthened during wakefulness thereby preventing continuously increasing cortical excitability (Frank, 2012; Tononi & Cirelli, 2012), while UP states may resemble "microstates" of wakefulness and play a role in the integration of awake experience into memories (Destexhe et al., 2007). Arousal -- the transition to wakefulness from sleep -- is mediated by increased activity in cholinergic nuclei of the brainstem, namely the cholinergic pedunculopontine tegmental nucleus and lateral dorsal tegmental nucleus, that project to the relay and reticular thalamus and to the cholinergic nucleus basalis of Meynert. In animals, brief electrical stimulation of the cholinergic nuclei of the brainstem produce desynchronization of the EEG lasting many seconds. Increased cholinergic input from the brainstem terminates thalamic hyperpolarization, increases activity flowing from the thalamus to cortex, and results in the depolarization of cortical neurons. The net effect of activation the cholinergic nuclei of the rostral pons– as was first described by Moruzzi and Magoun in their seminal description of the reticular activating system in 1948- is widespread desynchronization and acceleration of the EEG (Moruzzi & Magoun, 1949). Another subcortical structure with profound effects on seizure expression and suppression as well as in memory formation and modulation of executive functions is the substantia nigra pars reticulate and its GABA-sensitive output systems that reverberate through the basal ganglia (Veliskova & Moshe, 2006; O'Reilly, 2006).

The origin of slowing in the EEG of children with epileptic encephalopathy is not known. Possible etiologies are that the slowing results from areas of paroxysmal activity within cortex that are too small to detect on surface EEG, but that trigger aftergoing slow waves reflecting inhibition produced by interneurons within the cortex.

The persistence of slowing in the EEG of children with epileptic encephalopathy raises the question whether the encephalopathy is the result of insufficient depolarization or excessive or inappropriate hyperpolarization of the thalamus or cortex. Is – in effect - the cortex "asleep" during periods of wakefulness. This hypothesis can be tested, as on would predict that children with epileptic encephalopathies characterized by marked slowing in the EEG – would manifest the features of UP and DOWN cortical states, name alternating increases and decreases in beta-gamma activity that are locked to the phase of the slow voltage fluctuation. Termination of UP states may be mediated within cortex by somatostatin containing interneurons (Bragin et al., 2012).

Encephalopathy arising from disruption of normal cortical processing and possibly alteration of synaptic connections due to prolonged epileptic activity

The definition of Epileptic encephalopathy of the ILAE Task on Classification and terminology admits that epileptiform abnormalities themselves can contribute to a progressive disturbance in cerebral function (Engel, 2001). A condition in which impairment of cognitive status and motor functions, behavioural derangement, epileptic seizures are

related to the appearance of a peculiar EEG pattern, characterized by epileptic activity significantly activated during slow sleep, is represented by Encephalopathy with Status Epilepticus during Sleep (ESES), (otherwise labeled Continuous Spike and Waves during Sleep or CSWS) (Tassinari et al., 2012). Recent data on sleep physiology and homeostasis can contribute to formulate some hypothesis on the pathogenetic mechanisms involved in ESES Slow Wave Activity (SWA)is the principal neurophysiological marker of NREM sleep intensity. At a cellular level, SWA is characterized by a continuous alternation of the membrane potential between a hyperpolarized ‘up-state’ (with synchronous synaptic activities in the cortical network), and a depolarized ‘down-state’, during which neuronal discharges are prevented and associated with a global dysfacilitation in the cortico-thalamic network (Amzica & Steriade, 1998). The synaptic homeostasis hypothesis (Tononi & Cirelli 2006) suggests that the SWA is an active mechanism that restores the metabolic and functional efficiency of the brain, after the synaptic potentiation gathered during wakefulness. According to the synaptic homeostasis hypothesis, prolonged (every night for several months up to a number of years) epileptic activity could interfere with the changes in SWA that normally occur during sleep, and this may be causally related to impairment in cognitive functions and behaviour associated with ESES (Tassinari & Rubboli, 2006).

See Avanzini et al. in this supplement for further discussion.

Animal models of epileptic encephalopathies

Several animal models have been proposed to reflect key findings present in West syndrome, an archetypal epileptic encephalopathy (Galanopoulou, 2013). The multiple hit model described by Scantlebury and colleagues (Scanteblury et al., 2010) is a model of symptomatic West syndrome produced by unilateral hemispheric injury coupled with systemic administration of p-chlorophenylalanin, a serotonin deplete. Neonatal rats treated in this manner develop flexion and extension spasms and EEG changes characteristic of West syndrome, and subsequently manifest impaired learning. Interestingly, contralateral to the injured hemisphere, histology of the neocortex shows malformed and fewer GABAergic interneurons compared to controls. As discussed in an earlier section, knockdowns of TSC1, the gene implicated in tuberous sclerosis, is associated with increased activity in the mTOR pathway. Dysregulation of mTOR activity is observed in cortical dysplasias and malformations often associated with symptomatic West syndrome. Pulse application of rapamycin, an mTOR inhibitor, suppressed spasms and improved the cognitive outcomes suggesting of contributing role of ongoing spasm in the expression of the encephalopathy (Raffo et al., 2011). Enhancing GABAergic neurotransmission by administration of vigabatrin, which irreversibly inhibits the enzyme GABA transaminase responsible for degradation of GABA improves spasms, though only transiently, perhaps reflecting a loss of GABAergic interneurons reminiscent of a interneuropathy seen in autism or Dravet syndrome

Another model that has provided significant insights is the model produced via intracerebral chronic infusions of tetrodotoxin (TTX) for several weeks starting from the 10th day of life in rat pups. This leads to the development of spontaneous recurrent brief spasm-like seizures in adulthood (Frost et al., 2011. The seizures are characterized by brief extensor or flexor spasms; the ictal EEG pattern consists of an initial generalized, high amplitude, slow wave followed by an electrodecrement with superimposed fast activity. Spectral analysis with band pass filtering showed that the earliest and most intense high frequency discharges occur contralaterally to the infusion site where interictal high-frequency oscillations (HFOs) occur too. Microwire recordings shows that neuronal unit firing abruptly increases with the generation of HFOs during both ictal and interictal discharges (Frost et al., 2012. These data, together with the data from the multiple hit model may imply that neocortical networks may

be abnormally excitable in these two models. However, subcortical contributions must be elucidated because West syndrome may be caused by the abnormal interaction between cortical and subcortical structures. (Lado & Moshe, 2002).

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